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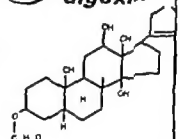
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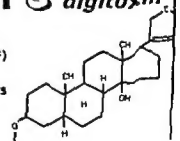
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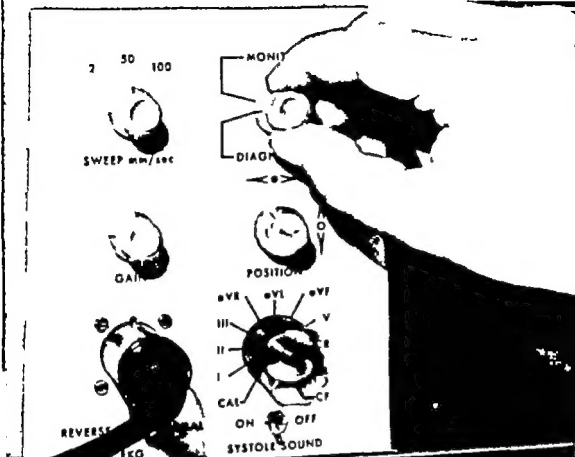
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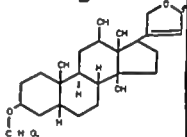
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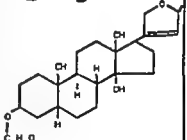
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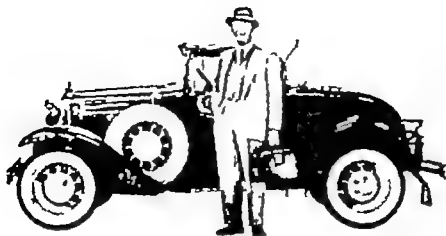
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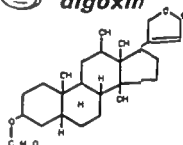
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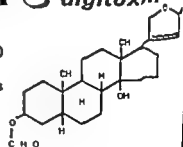
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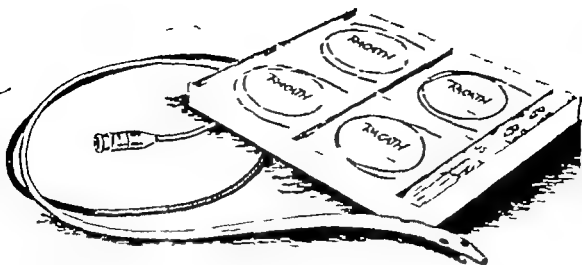
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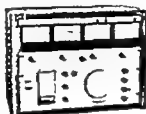
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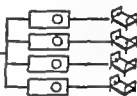
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Some aspects of circulatory
and respiratory functions in mammalsH. Bartels M.D.*
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On peut dire de grand progrès a été fait dans la connaissance

Claude Bernard

Studies in comparative physiology can open to the physician new aspects which although he has often read this page in the book of nature concerning Man have previously gone unnoticed. Suddenly he sees how fantastically diverse are the possibilities provided by nature, for example the ability of animals to satisfy their varying metabolic rates. Even consideration of this problem within the framework of the rather homogeneous class Mammalia furnishes one with amazing insight.

With the exception of his mental processes Man is a rather average mammal. His body weight is 10,000 times greater than that of the smallest mammal yet the elephant weighs 60 times more and the large blue whale weighs 2,000 times more.

As we learn from mathematics one can often derive an understanding of relationships better by observation of extreme cases. Therefore we will focus our attention preferably upon the very small and very large animals.

Unfortunately physiologic measurements on both extremely large and ex-

treinely small animals are fraught with methodological difficulties of all types. Measuring the cardiac output of a 12 gram shrew seems at present to be an almost impossible undertaking. Likewise the insertion of a heart catheter into a 7-ton unanesthetized elephant could become a dangerous venture should the animal with his agile trunk interest himself in the procedure or even worse in the operator. Nevertheless my friends Cecil Luck and Peter Wright in Uganda succeeded in measuring the cardiac output in immobilized African elephants. But normally information that can be obtained from these extreme animals is limited to procedures which can be more simply carried out such as the obtaining of morphologic data from dead animals and the measuring of metabolic rate and blood function which are meaningful to any studies of respiration and circulation.

The remarkable investigations performed by Francis C. Benedict in the nineteen thirties in Washington D.C. on the 3-ton Indian elephant Jap remain a famous example of this type of research. Benedict found the basal 24-hour production of heat of Jap to be 30,000 calories equal to that of 30 men. 1.4 kilogram of body

weight the elephant produces 13 calories whereas the human being produces up approximately 26 calories in 24 hours. This shows a lower metabolic intensity in the elephant than in Man.

On the other hand a shrew produces 0.005 calories per minute which is equal

to 0.5 calories per kilogram of body weight or more than 100 calories per kilogram in 24 hours.

Fig. 1 illustrates the increasing metabolic activity with decreasing body weight. In stead of the production of heat the consumption of oxygen is used as a basis of comparison. This figure demonstrates the fact known as the *law of diminishing metabolism*.

The mere establishment of a biological law is of course not an explanation of cause. To date no satisfactory theory has been advanced to explain this phenomenon. Conversely the fact of the matter alone drives the biologist in the pursuit of answers to some very exciting questions for example how the varying metabolic demands are met by the various species or restrictions, the topic how the call for oxygen is expressed by August Krogh⁴ is met.

Lung volumes and heart weights have been found to be linearly related to body weight in mammals (Fig. 2). Thus morphologically speaking we do not find any sign of adaptation to metabolic rate in the various species investigated. A linear relationship of tidal and stroke volumes

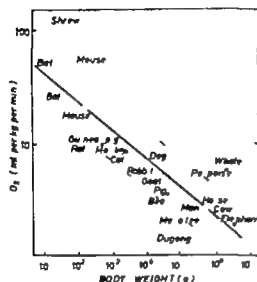


Fig. 1 Metabolic rate (milliliters of oxygen per kilogram per minute) as a function of body weight (From Bartel-Landert p. 599 1964)

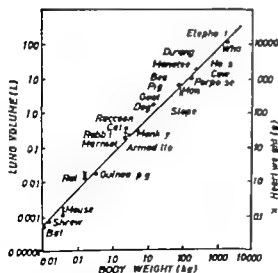


Fig. 2 Logarithmic plot of lung volume and heart weight as a function of body weight. Data on lung volumes from Tenney and Remmers; data on heart weights from Speck. Heart weights are represented by crosses.

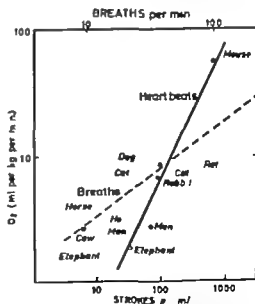


Fig. 3 Metabolic rate (milliliters of oxygen per kilogram per minute) as a function of frequency of respiration and the heart rate respectively (From Bartel-Landert p. 599 1964)

to body weight would mean that if alveolar ventilation and cardiac output were sufficient for the elephant they would be too low to meet the metabolic demand of the shrew. Respiration and heart rate provide an explanation increasing with decreasing animal size (Fig. 3). This suggests that ventilation and cardiac output are more closely related to the metabolic rate than to the body weight.

Greater ventilation and perfusion in the lung do not however necessarily mean that more oxygen is taken up by the blood. The diffusion surface of the lung could be too small; that is the diffusion capacity could still be insufficient for the metabolic demands. Tenney and Remmers¹⁴ have actually found that small animals possess alveoli which are smaller than those of large animals. This means that the total alveolar surface available for gas exchange is greater in small animals than in large animals. As a result of these increased diffusion areas relatively more oxygen and carbon dioxide can diffuse per unit of lung volume in small animals thus enhancing the intake of oxygen.

The increased amount of oxygen taken up in the capillaries of the lungs of small animals can perhaps be properly transported to the tissues by means of the relatively high cardiac output alone but this

is somewhat uncertain. In Fig. 4 the results of several measurements probably not all of which are reliable are plotted together and indicate this basic principle. However because of the unreliability of the measurements it is nonetheless difficult to say with any degree of certainty whether this is true. If cardiac output alone does not suffice to transport the increased quantity of oxygen then other mechanisms should make themselves evident reflected in the transport characteristics of the blood unless we have a complete thoracic frigate.

A glance at the hemoglobin concentration (grams per 100 milliliters of blood) does not show any reasonable relationship to body weight. However special characteristics of hemoglobin favoring the uptake of oxygen in the lung as well as the giving off of oxygen to the tissues illustrated by the well known oxygen dissociation curve do show differences between large and small animals.

The unloading tension for oxygen can be characterized by the half saturation for oxygen in the blood. This value is on the average higher in small animals than in large ones. The extreme cases of elephant and shrew demonstrate how this change in unloading tension becomes advantageous to the small animal (Fig. 5).

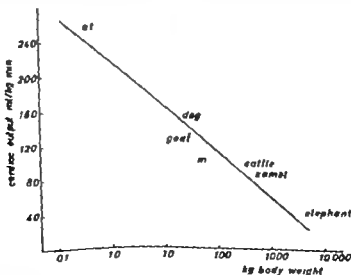


Fig. 4 Cardiac output (milliliters of blood per kilogram per minute) as a function of body weight. Data from Spector and for the elephant from Luck and Wright.

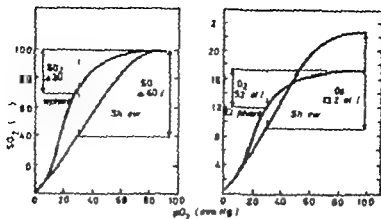


Fig. 5 (On the left is the oxygen dissociation curve of the blood of the shrew and the elephant. On the right is the oxygen dissociation curve of the blood of the shrew and the elephant. The curves are taken from Schmidt-Nielsen and Lennquist, 1961.)

The blood of the shrew is 60 per cent desaturated at an oxygen tension of 30 mm Hg, whereas the blood of the elephant is only 10 per cent desaturated. Furthermore, the higher hemoglobin content of the shrew's blood results in a higher arterial oxygen content. Thus, all in all, the shrew's blood at a tension of 30 mm Hg is able to give off 13 ml of oxygen to the tissues, whereas the elephant's blood at the same tension in delivers only 1 ml.

(One will now find that in these two extreme examples of land dwelling mammals, much in common also exists in the blood to support the increased need for oxygen.)

August Krogh⁴ postulated that the capillary density should reflect the cell for oxygen. This meant that capillary density should be increased in small animals. Recent investigations by Schmidt-Nielsen and Lennquist only slightly support Krogh's belief (Fig. 6). These authors think that other variable factors such as denervation, acclimatization to cold, and the amount of physical activity were too different in the species studied to allow any clear-cut relationship to be determined. On the other hand I am inclined to believe that in so far as small animals are concerned the relatively increased circulation and oxygen unloading capacity are of themselves sufficient to satisfactorily oxygenate the muscle tissue, which is capable of almost complete desaturation. It is interesting to note in Fig. 6 that only the bat has a significant increase in capillary density. Of all the species investigated the bat alone is the only animal that is able to fly, an accomplishment more strenuous than the other species are capable of.

Finally it has also been found that the cells of small animals have a much higher cytochrome oxidase activity and cytochrome C concentration, also furthering a higher turnover of oxygen within the tissues.

Now we have the impression that ventilation, cardiac output, lung surface area, oxygen unloading capacity, as well as cell enzymes together meet the increased

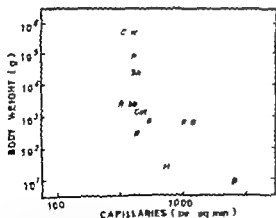


Fig. 6 Logarithmic plot of body weight versus number of capillaries per square millimeter of muscle (data from Schmidt-Nielsen and Lennquist, 1961.)

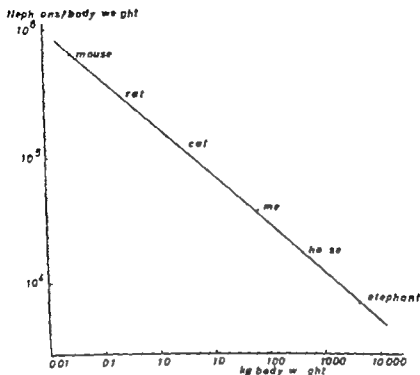


Fig. 7. Number of nephron per kilogram of body weight as a function of body weight (data from Adolph).

demands of increased metabolism in small animals is compared with large animals. Of course this is only one aspect of the problem. It should also be expected that the resorption surface of the gut and the excretory surfaces of the kidney would show a relationship to metabolic rate. The number of nephrons lend support to this view as Fig. 7 illustrates.

The question of why is there no larger land animal than the elephant is not answerable with any certainty although mechanical problems must undoubtedly be among the limiting factors. The much larger brachiosaur is no counterargument because much evidence lead us to believe that it spent its life in swamp thus utilizing the effects of buoyancy to support its huge body in a manner similar to that employed by whales. Also from the standpoint of metabolism it is difficult to conceive of any land animal exceeding the elephant in size since according to reports he is forced to spend almost 20 hours per day in the consumption of about 500 kilograms of grass and leaves. Any significantly larger elephant would be

forced in spite of its infinite reduction in metabolism to spend 24 hours a day eating thus requiring an even greater area in which to forage. To traverse this large forage area would alone require a vast expenditure of energy. Apparently heat regulation is also a limiting factor. Larger elephants or even present day elephants with a more intense metabolism would have great difficulty giving off the heat produced during muscular activity. The large ears of the elephant are actually special radiators which serve the process of heat regulation and would have to increase greatly in size. It is perhaps no coincidence then that African elephants which are larger have larger ears than their smaller Indian counterparts.

Perhaps the question of why there is no smaller mammal than the pygmy shrew can also be partially satisfied with the same answer applied to elephants. These minute mammals which have a body weight of about 2 grams must like the elephant also forage practically all night and day. The metabolism of these animals could not actually be reduced since they must

The "late systolic heartbeat" of pericardial effusion

Calvin F. Kay, MD*

Claude R. Joyner, MD

John Helwig, Jr, MD

Thomas F. Raymond, MD

Philadelphia, Pa

Several abnormalities of auscultation and palpation have been described in association with pericardial inflammation, effusion, constriction or calcification. Of these only three in so far as we are aware are systolic phenomena: reduction in intensity of the heart sounds and of the apex impulse, systolic friction rubs and clicks and the systolic retractions that precede the diastolic heartbeat of constrictive pericarditis. We have recently observed a patient with chronic pericardial effusion in whom a loud sound and easily palpable thrust were present late in systole. We believe that the mechanisms responsible for the production of these related phenomena bear some resemblance to those responsible for the "pericardial knock" frequently observed in the area of therapeutic pneumothorax in which the hypermobile heart suspended in air bumped against the precordium in systole.

The patient, a 36-year-old woman employed as a cashier in a cafe, was initially examined at the Hospital of the University of Pennsylvania in March 1963. She had had frequent episodes of palpitation and tachycardia documented to be attacks of paroxysmal atrial fibrillation for many years. She also described many episodes

of sharp pain rarely lasting more than a few seconds located in various areas of the anterior chest unrelated to exertion but possibly aggravated by breathing. These had been present from time to time for about 10 years and were at times so severe that she was hospitalized with suspected coronary occlusion on two occasions. The onset of her chief symptom, excessive fatigue with mild exertion, was difficult to date. It may have been present for 2 or 3 years but had been a serious handicap to her activities for about 6 months. Some sense of breathlessness was occasionally noted. She had never had cough, orthopnea or edema. A soft basal systolic murmur was first observed in 1954. An x-ray film taken at that time was reported to show slight cardiac enlargement which was again noted in films in 1957 and 1961. Another film taken Jan. 19, 1963, showed a large heart shadow and this persisted despite digitalis and diuretics. Examination on March 1, 1965, revealed a slender woman of 36 years. The blood pressure was 108/70 mm Hg with no paradoxical change with respirations. The lungs were clear, the neck veins and liver were not engorged and edema was not present. As indicated by percus-

on the heart was quite large. Well inside the left border a sharp thrust could be felt. This was originally identified as the apex impulse, but it was further inside the left border than would be expected. On auscultation it was immediately noted that the

thrust coincided with a very loud sound that seemed to be in time but not in location the first component of a widely split second sound. It could barely be heard at the base and was alternately very loud and relatively soft in successive beats with considerable regularity. When breathing was suspended this alternation disappeared and the sound was relatively soft with each beat. The first and second sounds were easily heard but not loud and a faint systolic murmur was audible in the pulmonary area.

In an effort to diagnose the nature of the patient's illness and mechanisms responsible for the unusual auscultatory finding, a number of additional studies were carried out. The blood count, serologic tests, urinalysis, serum electrolytes, and a series of lupus erythematosus preparations were normal or negative. The chest x-ray film (Fig. 1) showed generalized cardiac enlargement. On fluoroscopy with image intensification the cardiac shadow was almost motionless but a mass with ill defined limits could clearly be seen to move retrochly within the central portion of the total cardiac shadow, confirming the suspicion that a pericardial effusion was present. This was further confirmed by a



Fig. 1 Chest x-ray film of the patient March 7, 1965

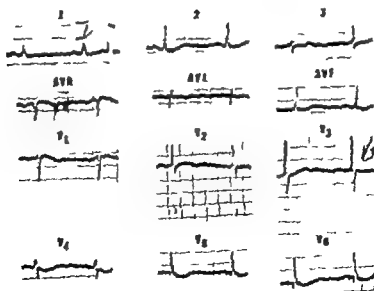


Fig. 2 Electrocardiogram March 7, 1965. Minimal changes compatible with digitalis therapy.

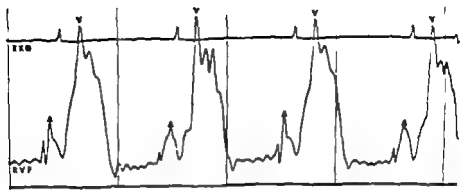


Fig 3 Right ventricular pressure. Large A waves with alteration of A and of V pressure curves

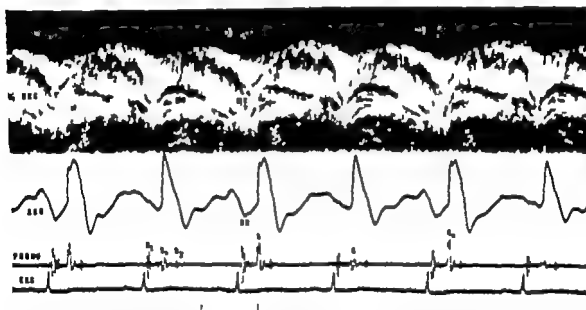


Fig 4 Triple contour of ultrasound (UAG) record of a tented leaf of mitral valve (M). Mitral opening (MO) and closure (MC). Prominent A wave, systolic retraction (SR) and late systolic thrust of a pericardial effusion (ICG). Systolic sound (S) at onset of rapid outward movement of systolic thrust. Alteration of all components except ECG.

radioisotopic scan and by ultrasound. The electrocardiogram showed some RST depressions that could be ascribed to the digitalis which she had been receiving. The amplitudes of all electrocardiographic components were normal (Fig 2).

On right heart catheterization oxygen saturations were all normal with no evidence of shunts. Right ventricular systolic and diastolic pressures were mildly elevated (40/7 mm Hg) as was the pul-

monary arterial pressure (40/15 mm Hg). A prominent A wave was present in the right ventricular pulse curve (Fig 3). A dye-dilution curve (superior vena cava to left brachial artery) confirmed the absence of a shunt. The cardiac index was calculated at 1.99 L/min/m^2 , markedly reduced from the normal of 3.25 ± 0.25 . Two selective cineangiocardiograms were obtained. These confirmed the presence of a pericardial effusion. The left atrium ap-

peared to be a little enlarged but otherwise no structural abnormalities were defined. Active contraction of the ventricular chambers was apparent.

Simultaneous recordings were then made of the heart sounds and aortic aorticogram (ACC) (recorded from the point of maximum thrust inside the apex of the heart

shadow) together with the ultrasonic cardiogram (UHC) and the electrocardiogram (EKG) (Fig. 4). The alternating beat to beat variations are obvious in all except the EKG which remains unchanged. The extra sound S_x is in mid to late systole with the timing varying slightly on various tracings, a phenomenon which

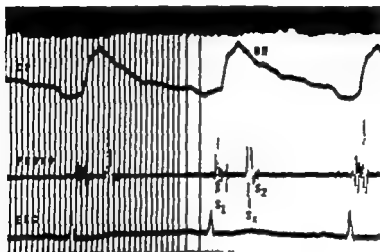


Fig. 5 Carotid pulse (CP) with diastolic notch (DN) immediately preceded by S_4

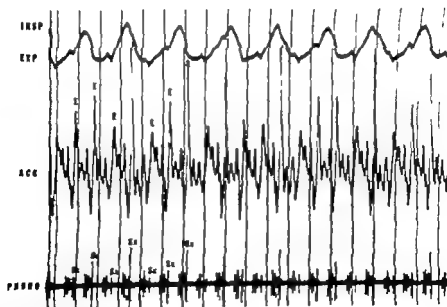


Fig. 6 Low S_x and large apex thrust (E) in late inspiration and early expiration. S_x and small apex thrust (E) after expiration and in early inspiration.

has also been noted previously with the pericardial knock. The first heart sound which precedes the large S_2 is louder than in the beats in which S_2 is small. S_2 large or small is seen to occur during the sharp rise in outward thrust of the chest wall. The duration of outward thrust is longer in the large S_2 beats than in the small ones. The UKG beam on the anterior leaf of the mitral valve shows coincidence of the closure of the valve (AIC) with the first sound as is normal. Mitral valve opening (AIO) follows S_2 by a normal interval. During the period of diastole the triple movement of the valve (A1, 2, 3) resembles that found by one of us (CJ) in various disorders associated with decreased ventricular diastolic compliance.

In subsequent records S_2 was found to slightly precede the dicrotic notch of the carotid pulse curve as expected (Fig. 5). Additional studies (Fig. 6) showed that the intensity of S_2 and of the associated precordial thrust correlated directly with the phase of respiration. Maximum intensities were at the peak of inspiration or on the downslope of expiration and minimal intensities occurred at the end of expiration or during the early rise in inspiration. This confirmed earlier clinical observations. By a coincidence in most of the recordings the resting respiratory

rate was consistently very near to half the pulse rate. The respiratory effect is visible in the alternate variations of the A waves of the right ventricular pressure curve, the variations during late diastole in the apexcardiogram and in the UKC and probably in the variations in intensity of S_1 .

Because the tuberculin test was very strongly positive in lowest dilution it was decided to employ a therapeutic trial of antituberculous drugs. After 1 month the patient returned to the hospital her symptoms and findings unchanged. A thoracotomy was then performed by Dr Gordon Danielson. The pericardium was slightly thickened and contained about 900 cc of hazy straw colored fluid. The anterior pericardium was removed and the patient recovered uneventfully. Sections of the pericardium were reported to show a nonspecific pericarditis and cultures of the tissue and fluid showed no evidence of tuberculosis or other infectious agent. Postoperatively the unusual sound had disappeared. Several of the studies were repeated. The apexcardiogram heart sounds and UKG of the mitral valve movements were now all normal (Figs. 7 and 8).

It is concluded that the systolic thrust and related loud late systolic sound were

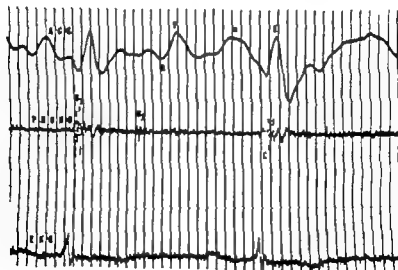


Fig. 7 Postoperative appearance of S_2 and relatively normal ACG

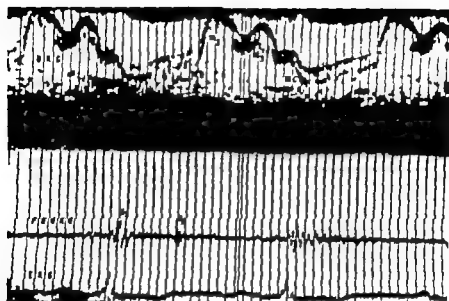


Fig. 8. Interior pericardial knock (ICG) and interior deflection (M₂) of mitral valve. The upper and middle tracings are the interior pericardial knock (ICG) and the lower tracing is the ECG.

the result of a forward thrust of the heart suspended in fluid against the overlying pericardium and that in turn against the chest wall. The remarkable degree of variation in these related phenomena with respiration suggests the possibility that as the interior pericardium is drawn down by the descending diaphragm the heart is brought closer to it in a better position to strike it during systole. This could also account for the increased intensity of the first sound. However the respiratory variation in the atrial filling wave and the change in the systolic pressure curve in the right ventricle suggest that the increased intensity of these phenomena relate rather to increased right ventricular filling during inspiration. This combination of thrust and sound must not of course be confused with the diastolic heart beat described by Skoda³ in 1852 which Wood⁴ recognized to be the result of the forward thrust of the heart propelled by a high venous pressure through an interior window of an otherwise constrictive pericardium. This sound could hardly be con-

fused with a systolic click or a friction rub. The mechanism bears some analogy as noted above to the sound and thrust of the pericardial knock of pneumothorax and also to the late systolic sound and thrust rarely observed as a result of the paradoxical movement of the apex of an apical aneurysm. That this late systolic thrust and sound is not a common observation in pericardial effusion seems to be surprising, but our experience has been that it is not.

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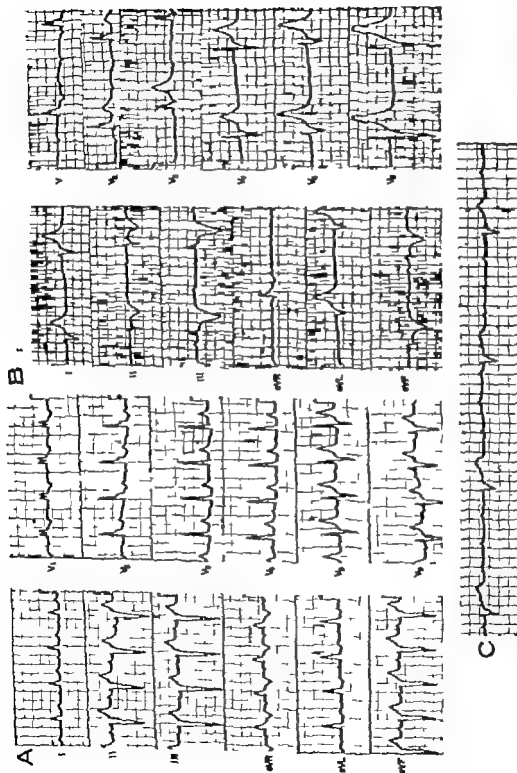


Fig 1. ECG taken on Dec 16 1958 shows normal AV conduction with intraventricular block. B R and taken Feb 24 1959 during a period of complete heart block. C R and taken on Nov 24 1959 7 minutes after atropine 1 mg. complete block unaffected by atropine

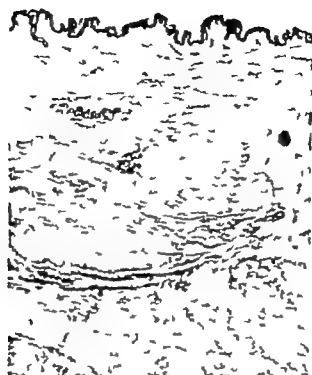


Fig 2 Biopsy of skin. Hematoxylin-eosin stain. X47. Note the marked increase in relatively atypical collagen in the deep corium and subcutaneous tissue.

1959 because further cardiac enlargement was noted the aortic pressure was 170 mm of mercury and the correlation time (Hechbolim) was 30 seconds. Digitalization was cautiously begun. After oral dosage of between 0.5 and 1.0 mg of digoxin he gradually returned to normal rhythm. A marked effective intracardiac premature beats and a pulse rate of 26. A more regular rhythm returned when the drug was stopped. Because of this adverse effect the patient was never fully digitalized. In October 1959 he was permitted to go home and in a syncopal attack on Nov 17 1959 he was brought to Lutheran Hospital and pronounced dead on arrival. An autopsy was performed at this hospital.

Biopsy of the skin and muscle (taken Jan 1959). There was a marked proliferation and straightening of the collagen fibers in the deep corium and the subcutaneous tissue (Fig 2). Very few fibroblasts were present in this area. There was infiltration of mononuclear cells around the vessels and some of the skin appendages. The vessels and the epithelium however showed no changes. The muscle showed no changes.

Postmortem examination

Aside from the findings in the heart the pathologic diagnoses were (1) Chronic esophagitis with leukoplakia and marked fibrosis of the muscularis. (2) Marked fibrosis of the muscularis of the intestine.

(3) Pulmonary fibrosis and emphysema. (4) Marked chronic passive hyperemia (a) of the lungs (b) of the liver with central necrosis (c) of the spleen with fibrosis and (d) of the kidney with cloudy swelling. (5) Local pyelonephritis. (6) Pulmonary edema with hemorrhage. (7) Acute degeneration of large arterioles in lungs heart kidney and gastrointestinal tract.

The heart

GROSS EXAMINATION. The autopsy was performed 12 hours after death. The opened heart was immersed in 4 per cent formaldehyde in toto and sent to one of us (M.L.).

The heart was enlarged and weighed 431 grams (fixed). The pericardium over the right ventricle and both atria showed large areas of thickening, and smaller more discrete plaques were present on the anterior wall of the left ventricle. The right atrium was enlarged and its wall was thickened. Hemorrhagic zones were present in the right atrial appendage. The tricuspid orifice was enlarged.

The right ventricle was enlarged and

its muscular wall was thinned in the conus region. Here a considerable layer of fat penetrated from the epicardium almost to the endocardium. The endocardium of this chamber showed focal hypertrophy, and the pulmonary valve presented increased hemodynamic changes. The left atrium was questionably enlarged but its wall was thicker than normal. The mitral valve showed nodose thickening at the line of closure and at the edge with some thickening of some of the chordae. The left ventricle was slightly enlarged but its wall was of average thickness. Its endocardium was thickened at the base. The myocardium on section showed fibrotic strands. The right coronary artery was somewhat narrowed.

MICROSCOPIC EXAMINATION

Methods. The entire heart including the entire conduction system was studied histologically in a manner previously described.²⁴ Specifically, the S-A node and its approaches were serially sectioned at 7 μ and every twentieth section was retained. The approaches to the A-V node, the A-V node, the penetrating portion of the bundle and the beginning of the branching portion were serially sectioned at 10 μ and all sections were retained. The remainder of the branching bundle and left and right bundle branches up to the muscle of Langerhans

were serially sectioned and every tenth section was retained. The remainder of the right and left bundle branches up to the region of the moderator band was serially sectioned and every twentieth section was retained. The remainder of the septum and walls were cut into blocks and two sections were cut from each block. All of the above mentioned sections were alternately stained with hematoxylin-eosin and elastic van Gieson stains. In this manner 4850 sections were examined. Also several sections were stained for metachromasia by the Hotchkiss method for glycoprotein and by the Congo red method for amyloid.

Findings

Left Ventricle.—The trabecular area in the subendocardial third of the myocardium was diffusely replaced by a loose tissue containing collagenous and elastic fibers. In these regions there was a dearth of Purkinje fibers and those that were present showed degenerative changes. The subendocardial portion of the myocardium at the base showed marked replacement by hyalinized connective tissue (Fig. 3). The remainder of the myocardium presented a proliferation of fine and coarse elastic and collagenous fibers both perivascularly and between the muscle fibers with scattered areas replaced by vascular and nonvascular



Fig. 3. Section through the base of the septum in the left ventricle showing fibrosis and hyalinization in the subendocardial region. Weigert van Gieson stain X22.

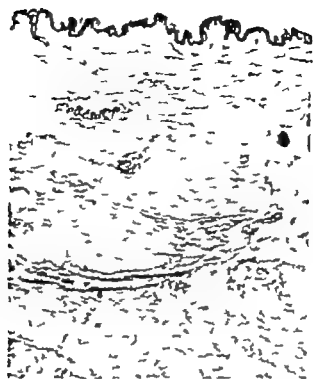


Fig 2 Deep ulcer. Hematoxylin-eosin stain $\times 400$. Note the presence of relatively acellular collagen in the deep portion and ulcerated surface.

1959 because further cardiac enlargement was noted the end diastolic pressure was 170 mm Hg and the circulation time (Dextran) was 80-second. Digitalization was instituted by oral dosage of between 0.5 and 3.0 mg of digoxin. A regular rhythm was noted with moderate ventricular premature beats and a pulse rate of 26. A more regular rhythm returned when the drug was stopped. Because of this adverse effect the patient was never fully digitalized. In October 1959 he was permitted to go home and in a syncope attack on Nov 17 1959 he was brought to Lutheran Hospital and pronounced dead on arrival. An autopsy was performed at this hospital.

Biopsy of the skin and muscle (taken June 1957)
There was a marked proliferation and straightening of the collagen fibers in the deep corium and the subcutaneous tissue (Fig 2). Very few fibroblasts were present in this area. There was infiltration of mononuclear cells around the vessels and some of the skin appendages. The vessels and the epidermis however showed no changes. The muscle showed no changes.

Postmortem examination

Aside from the findings in the heart the pathologic diagnoses were (1) Chronic esophagitis with leukoplakia (2) Marked fibrosis of the muscularis (3) Marked fibrosis of the muscularis of the intestine

- (4) Pulmonary fibrosis and emphysema
- (5) Marked chronic passive hyperemia
- (6) of the lungs (b) of the liver with central necrosis (c) of the spleen with fibrosis and (d) of the kidney with cloudy swelling
- (7) Focal pyelonephritis (8) Pulmonary edema with hemorrhage (9) Acute degeneration of large arterioles in lungs heart kidney and gastrointestinal tract

The heart

GROSS EXAMINATION The autopsy was performed 12 hours after death. The opened heart was immersed in 4 per cent formaldehyde in toto and sent to one of us (V.L.).

The heart was enlarged and weighed 451 grams (fixed). The epicardium over the right ventricle and both atria showed large areas of thickening and smaller more discrete plaques were present on the anterior wall of the left ventricle. The right atrium was enlarged and its wall was thickened. Hemorrhagic zones were present in the right atrial appendage. The tricuspid orifice was enlarged.

The right ventricle was enlarged and

myocardium and endocardium showed a great infiltration of fat tissue

Atria—There was a marked proliferation of the elastic and collagenous tissue pervascularly and between muscle cells of both atria with occasional degeneration of the myocardial cells (Fig 5) and hemorrhage in the right atrium

Conduction System—

S-A node There were no changes

Approaches to the S-A node There was marked proliferation of the elastic and collagenous tissue pervascularly and between muscle cells in the myocardium with occasional acute degeneration of muscle cells, hemorrhage and chronic inflammation. Some arterioles showed marked thickening of the internal elastic lamella with fragmentation of the elastic tissue of the media and proliferation of collagen

of the adventitia. Occasionally there was also proliferation of the intima

Approaches to the A-V node Focal proliferation of the elastic and collagenous tissue of the myocardium with degeneration of muscle cells and an infiltration of mononuclear cells was present

A-V node The node was normal in its initial portion. However more distally the elastic network around the cell became progressively more accentuated (Fig 6)

A-V bundle penetrating No burn was present around most of the bundle; the latter was more or less fused with the central fibrous body (Fig 7). The cells of the bundle close to the connective tissue of the central fibrous body were greatly swollen, vacuolated with pyknotic nuclei (Fig 8) in some cases. This process was more severe distally. Parts of the bundle



Fig 6



Fig 7

Fig 6 Section through the A-V node showing elastic tissue of most of the node with the exception of that adjacent to the central fibrous body. Weigert-Gieson stain X40. Arrows point to the node.

Fig 7 Section through the penetrating portion of the A-V bundle showing absence of the elastic tissue in its portion. Elastic tissue is present in the lower portion but not the uppermost portion. Weigert-Gieson stain X40. Arrows point to the bundle.



Fig. 8. Section through the upper part of the penetrating portion of the AV bundle showing marked acute degenerative changes in the Purkinje cell adjacent to the central fibrous body (hematoxylin-eosin stain $\times 154$).

showed accentuation of the elastic network whereas parts adjacent to the central fibrous body showed a decrease in elastic tissue (Fig. 7).

AV bundle branching. This portion was very short and showed changes similar to those seen in the distal portion of the penetrating portion.

Bifurcation. The acute degenerative changes mentioned above were very severe here. This was accompanied by considerable accentuation of the elastic network.

Right bundle branch. The right bundle branch showed marked proliferation of elastic and collagenous fibers which replaced part of the structure with acute degeneration of cells in all three parts (Fig. 9). This was especially marked in the third part.

Left bundle branch. The elastic and collagenous network was proliferated in the beginning with degeneration of Purkinje cells (Fig. 10). More distally there was more marked fibrosis (Fig. 10B). The degeneration of cells was seen throughout the left bundle branch up to the periphery. In some areas there was a dearth of Purkinje cells and an infiltration of lymphoid cells. The terminal Purkinje cells likewise showed marked degeneration.

Discussion

Pathologic changes in the heart in scleroderma were first alluded to by Hecht¹. Cardiac involvement in a clinical sense does not occur frequently.²⁻¹² The case for primary myocardial involvement in systemic scleroderma has been well argued^{4,6,13-17} with a convincing although limited clinical demonstration. A number of secondary modes of cardiac derangement may complicate and even dominate the picture: pulmonary hypertension,¹⁸⁻²⁰ systemic hypertension and hypertensive heart disease, the (probably) rarer involvement of coronary arteries¹⁴ and at least in the male the ubiquitous incidental association of coronary atherosclerosis. Lesser degrees of direct myocardial involvement are likely to be recognized in proportion to the frequency of search and the sensitivity of the index used even though clinical manifestations may be lacking ascribed to other features of the disease or to other coexisting disorders.

Our case clinically falls into the category of generalized scleroderma with cutaneous, gastrointestinal and cardiac findings. This is confirmed by the biopsy of the skin and the autopsy findings. The biopsy of the skin revealed an overgrowth of dense



Fig. 9. Sections through the right bundle branch. A End of first portion showing fibrous and elastic tissue with partial replacement of the bundle. Hematoxylin-Gieson stain $\times 40$. B Second portion of right bundle branch showing replacement of most of cells by fibroblastic tissue and degeneration of the remaining cells. Hematoxylin-Gieson stain $\times 255$. C Junction of second and third portions of right bundle branch showing fibroblastic replacement of part of bundle with degeneration of the remaining cells. Arrows point to the right bundle branch.

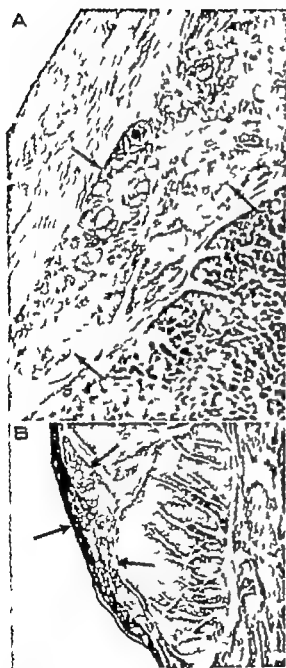


Fig. 10 Sections through the left bundle branch. A Beginning portion showing fibroelastic replacement of parts of the bundle with degeneration of many of the remaining cells. Hematoxylin eosin stain $\times 157$. B Bundle further down. Weigert van Gieson stain $\times 41$. Arrows point to the left bundle branch.

straight relatively acellular collagenous tissue in the deep corium and the subcutaneous fat tissue. This deep location of the process has been documented by Allen. Autopsy revealed chronic esophagitis with leukoplakia and fibrosis of the smooth muscle of the esophagus and the intestines in addition to the finding in the heart.

The heart showed diffuse fibroelastosis of the myocardium with replacement of most of the subendocardial third of the myocardium of both the left and right ventricles by fibroelastotic loose and dense connective tissue. Likewise such areas were found elsewhere in the myocardium and subepicardially. These areas were mostly unrelated to vascular changes and the relatively mild narrowing of the right coronary artery would not account for these changes. The lack of hemorrhage may be an added factor in favor of this interpretation.

The findings of an encysted trichina in the muscle biopsy does not warrant the concept of the myocardial findings being the end stage of so-called chronic trichinous myocarditis. In the first place there was no reaction about the cyst and hatched trichinosis is found in a considerable percentage of the population. Second it is the considered opinion of most workers⁶ that trichinosis produces an acute myocarditis which either is fatal or heals within 6 weeks. Only a few cases have been documented as ending fatally after 10 months. Furthermore acute trichinous myocarditis responds to steroids whereas no such reaction was found in this case.

The findings in the conduction system (Fig. 11) may be closely correlated with the electrocardiographic findings. The early intraventricular conduction abnormality may be explained by the progressive fibrotic replacement of the myocardium throughout the ventricles. This was followed by intraventricular block with a right bundle branch block pattern which is related to the progressive fibroelastotic replacement and more recent degenerative changes in the right bundle branch. Although the left bundle branch showed similar changes because of its wide distribution these changes were not manifested electrocardiographically until later.

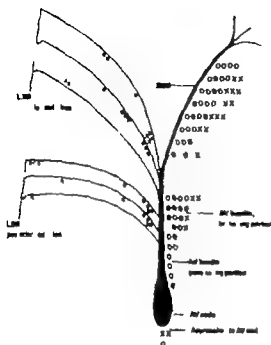


Fig. 11. Diagrammatic sketch of the conduction system showing pathologic change. X = Old change, O = Recent change.

when complete A V block occurred. The restoration of normal A V conduction time after periods of complete block which continued to occur for over 11 years after the onset of syncopal attacks is further indication that the A V block was largely produced by progressive destruction of both right and left bundle branches. The change in the A V node and bundle of His are of a lesser magnitude than those in the bundle branches. The influences of the former changes cannot be excluded since persistent P R prolongation and 2:1 block did occur before complete block was chronically established. Some involvement of sympathetic neuroeffector endings is also possible in view of the period of varying A V conduction and of the atrial and ventricular irritability which was noted even before Isuprel was used. Involvement of the bundle branches to produce A V block is well known and the extent of the pathologic change is in keeping with other cases in which heart block has been produced.⁷

The pathologic process in the bundle of His and bundle branches sheds some light

on the assumed basic change occurring in the heart in generalized scleroderma. At present it is assumed that there is a marked overgrowth of collagen which results in secondary degenerative changes in the myocardium. This is seen best in the A V bundle.

The A V bundle normally is surrounded by a sheath or bursa⁸ which apparently permits it to lie relatively loose in the central fibrous body. This sheath is considerably replaced by connective tissue in our case and apparently correlated with this are the severe acute degenerative changes in the cells of the bundle. In the areas close to the central fibrous body the degeneration is most intense whereas it is less so elsewhere in the bundle. And it is precisely adjacent to the central fibrous body that the elastosis is least pointing to the probably secondary elastic transformation of connective tissue related to changes in tension.

Apart from electrocardiographic manifestations of chamber hypertrophy the frequent occurrence of left bundle branch block, right bundle branch block and partial heart block and the occasional occurrence of complete heart block in scleroderma heart are probably best explained as involvement of the bundle branches by the collagenous overgrowth with secondary degeneration although some cases of partial or complete heart block may be due to the changes in the bundle itself.

Summary

A case of generalized scleroderma with maximal involvement of the heart is reported. Electrocardiographically there were progressive changes ending in complete A V block. Comprehensive studies of the conduction system revealed marked old replacement of both bundle branches by fibroelastic tissue which is considered to be the cause of the block. The acute changes in the bundle confirm the prevailing thesis that collagenous proliferation is responsible for the myocardial changes.

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Prolonged depressing effect of premature supraventricular beats

A mechanism causing transient ventricular standstill

William Dressler M.D.*

New York N. Y.

Premature atrial beats which disturb the sinus rhythm are usually followed by a pause which although noncompensatory is longer than the initial cycle.^{1,2} The prolongation is accounted for by the time required by the premature excitation to reach the sinus node.³ In addition it has been shown that on occasions the premature stimulus by breaking into the pacemaker exerts a depressing effect.⁴ The resulting slowing down of the sinus node which is manifest through one or several sinus cycles⁵ is not dependent on vagus action for it has been observed also in the atropinized experimental animal.⁶ The depressing mechanism is probably of the same kind as that responsible for the preautomatic pause which after inhibition of the regular pacemaker or interruption of A-V conduction precedes activation of the lower center. Edelst and associates⁷ have shown in patients with inserted pacemakers in whom either the right atrium or the right ventricle was stimulated electrically that with an increasing rate of stimulation there was a progressive lengthening of the escape interval of the patient's own pacemaker. This temporary depression of the formation of impulses became more marked in digitalized patients and was then probably associated

with a depression of conduction of impulses.

Premature atrial beats may show a disturbance of A-V conduction (either delay or failure).⁸ The disturbance is exaggerated when conduction of the regular beats is unimpaired. The earlier the premature excitation occurs the more likely that it finds the junctional tissues in the refractory state. Even blocked premature atrial beats may have a profound influence upon the production of impulses and A-V conduction in the following beats.⁹ Langendorf¹⁰ has stressed the role played by concealed conduction in the development of these disturbances. Observations to be reported here seem to indicate that a depressing effect of premature excitations upon A-V conduction may also be a factor.

Premature atrial beats do not commonly exert a depressing action. Such an effect depends on a hypodynamic state of the heart. It has been observed in the experimental animal when experimentation was prolonged or when the vitality of the heart was reduced by the effect of cold asphyxia or quinidine.¹¹ In man likewise inhibiting effects upon the pacemaker seem to occur in the presence of heart disease.

In the following report 4 cases are described which demonstrate a marked and sustained depressing action of pre-

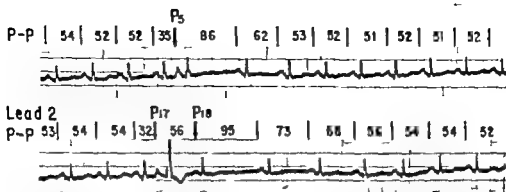


Fig 1 Case 1 The two strips are continuous. A regular sinus rhythm with a cycle length ranging from 0.51 to 0.54 sec is interrupted by premature atrial beats (arrows). P5 is followed by a pause which is more than compensatory and the next sinus cycle is still prolonged. P17 and P18 are both premature. The returning cycle is 0.90 sec long that is more than compensatory and the following three sinus cycles are still longer than the average sinus period.

mature atrial beats upon the pacemaker and it is believed also upon A-V conduction.

Report of cases

Case 1 N.E. a 68 year old man suffered an extensive myocardial infarction 6 months prior to examination.

Fig 1 shows a regular sinus rhythm with an average rate of 113 per minute. The length of the sinus cycle varies from 0.51 to 0.54 sec. The sinus rhythm is interrupted by premature atrial beats (P5, P17 and P18). The coupling of P5 is 0.30 sec, the length of the returning cycle measures 0.86 sec. The combined lengths of these periods are longer than two regular cycles. The sinus period which follows the returning cycle is still prolonged, measuring 0.62 sec.

P17 has a coupling of 0.32 sec. Its ventricular complex is aberrant in shape. P18 is probably also premature since it falls after an interval of 0.36 sec instead of an expected prolonged pause similar to that following P5. Its ventricular complex is normal in shape because the extrasystole falls later in diastole and the refractory period following P17 is short because of the short length of the preceding cycle. The sinus cycle which follows P18 measures 0.90 sec, that is it is of more than compensatory length. The next three sinus cycles are also prolonged, measuring 0.73, 0.68 and 0.56 sec, respectively.

COMMENT. In this case premature atrial beats arriving early in diastole are followed by longer than compensatory pauses. This is due to a depressing effect upon the pacemaker which is more intense and protracted when two premature beats occur in sequence. Delay in the production of impulses affects then several sinus periods.

Case 2 L.F. a 64 year old man suffered from calcific aortic stenosis and congestive heart failure.

Fig 2 shows four strips which form a continuous tracing. In the top strip A a regular atrial tachycardia with inverted P waves and 2:1 A-V block is noticed. The atrial rate is 130 per minute. The cycle length measures 0.46 sec. P13 is a premature atrial contraction which falls after an interval of 0.31 sec. It is followed by an atrial pause which lasts 13 sec and is interrupted by nodal escaped beats. Up right P waves appear in strip C (arrows) in intervals which gradually decrease from 2.14 to 1.90 sec. The first of these P waves is blocked, the second and third are apparently conducted, the former with a P-R interval of 0.20 sec and the latter which falls earlier in diastole with a P-R interval of 0.52 sec. In D the first P wave is not conducted because of interference with a nodal escape. Then a regular sinus rhythm is established with a cycle length of 0.91 sec and a P-R interval of 0.19 sec.

COMMENT. In this case an atrial tachycardia with A-V block is abruptly brought

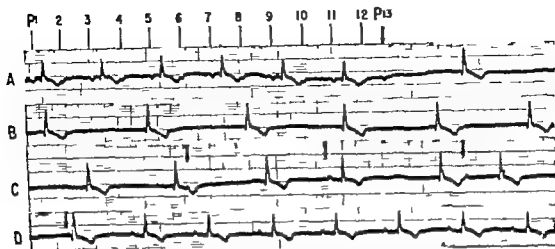


Fig. 2 Case 2 Strips A-D are continuous. Strip A shows a regular atrial tachycardia with 2:1 AV block. P13 is premature and appears to bring to a halt the atrial tachycardia. An atrial pause of 13 sec. ensues which is interrupted by nodal escaped beats. In C upright P waves (arrows) appear, the second and third of which are conducted. In D the first P wave is blocked because of interference with the following nodal escaped beat. Then a regular sinus rhythm sets in.

to a halt after a premature atrial contraction. The long atrial standstill that follows is due to the combined depressing effects of the premature atrial beat and the preceding atrial tachycardia.

Case 3. L.A., a 65 year old woman suffered from Type II AV block with Adams-Stokes syndrome which necessitated implantation of a pacemaker. Fig. 3A was taken prior to implantation. It shows two continuous strips of a regular sinus rhythm with an average rate of 111 per minute. On two occasions the sinus rhythm is interrupted by a premature atrial beat (arrows) which initiates a ventricular standstill.

In the upper strip the sinus cycle measures 0.50 sec. The premature atrial contraction has a coupling of 0.36 sec. Not only is the premature P wave blocked but also the two following sinus excitations although the first sinus cycle is prolonged measuring 0.62 sec. and the following sinus periods measure 0.50 sec. the same as the initial cycles. The first P wave after the ventricular standstill is blocked because it follows closely an escaped beat.

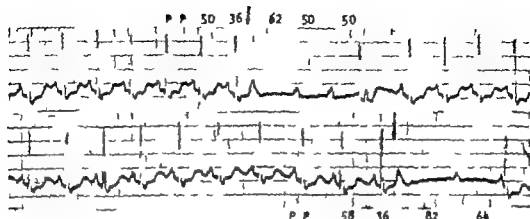
In the lower strip of Fig. 3A the length of the sinus period has increased to 0.58 sec. A premature atrial contraction (arrow) arrives after a pause of 0.36 sec. and is blocked. The returning cycle measures

0.82 sec. and the following sinus period 0.64 sec. Although these cycles are longer than the initial sinus period affording a longer than average rest period no AV conduction takes place. The ventricular standstill is concluded by a nodal escaped beat.

In the original electrocardiogram there were more than thirty premature atrial beats each of which initiated a period of ventricular standstill due to AV block.

COMMENT. In this case of Type II AV block regular sinus rhythm with normal AV conduction is frequently interrupted by a premature atrial beat which is blocked. Although the following sinus cycles are prolonged one or two sinus excitations after the premature beat are not conducted to the ventricle. This is thought to be due to a depressing action exerted upon AV conduction by the premature atrial excitation which partially penetrates into the junctional fibers. Pick and associates have offered a different interpretation in a similar case. They thought that AV conduction of the sinus beats was possible only because at a certain length of the sinus period the stimuli fell into the super-normal phase of AV conductivity. This condition was disturbed by the occurrence of premature atrial beats so that not only was the premature stimulus blocked but

A



B

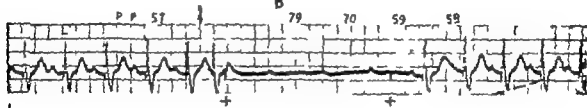


Fig 3 (Ca) The α trip are *interruption* in the *upper strip* a regular sinus rhythm with a cycle length of 0.50 sec is interrupted by premature P waves which fused with the preceding T wave. The returning cycle is 0.50 sec and the following sinus period measures 0.50 sec. Not only is the premature atrial beat blocked but also the two following sinus contractions. The resulting ventricular standstill is concluded by a nodal escaped beat. In the lower strip the α trip measures 0.58 sec. Following a premature atrial beat (which the returning cycle is 0.57 sec and the next sinus period measures 0.64 sec) the premature atrial beat and the following sinus period are blocked. The ventricular standstill is concluded by a nodal escaped beat. B Ca 0.57 regular sinus rhythm is interrupted by a premature beat (arrow) of either atrial or nodal origin. The initial cycle measures 0.57 sec. Although the following sinus period are prolonged three P waves are blocked. Then a normal sinus rhythm with normal AV conduction is restored (vertical lines are marked by +).

also the following normal sinus stimuli. Supernormality was restored by escaped beats which were conducted (concealed) in a retrograde fashion to a region of unidirectional block. This interesting and persuasive interpretation could not be applied to our next case (Fig 3B) in which AV conduction was restored with out the intervention of an escaped beat.

Case 4 MR a 50 year old man suffered from hypertensive heart disease. Fig 3B shows a regular sinus rhythm with a cycle length ranging from 0.57 to 0.60 sec. The P-R interval measures 0.18 sec. The sixth beat (arrow) is premature arriving after an interval of 0.37 sec. It is of supraventricular type either atrial or nodal in origin. A premature atrial wave cannot be distinctly made out in the pre-

ceding T wave. The premature excitation is conducted to the ventricle and it probably reaches and disturbs the sinus node for not only is the returning cycle obviously prolonged but also the following two sinus cycles which measure 0.79 and 0.70 sec respectively. Hence it is assumed that the premature atrial excitation depresses the sinus action. In spite of the increased duration of the sinus cycles three P waves following the premature beat are blocked. The fourth regular P wave is again normally conducted to the ventricle and normal sinus rhythm and AV conduction are restored.

COMMENT: A regular sinus rhythm with normal AV conduction is interrupted by a premature beat of supraventricular type. The latter is transmitted to the

sinus node and depresses the production of sinus impulses for three successive periods. Although prolonged duration of the sinus cycles affords a longer recovery time for the junctional tissues three P waves following the premature beat are blocked. Hence it is assumed that the premature beat depresses not only the regular pace maker but also A-V conductivity.

Summary

Four cases are reported which demonstrate a sustained depressing effect of premature supraventricular beats upon the pacemaker. In one case atrial tachycardia with block is brought to a sudden halt after a premature atrial beat.

In two instances premature supraventricular excitations which interrupt a regular sinus rhythm are followed by A-V block of one or several sinus excitations. Disturbance of A-V conduction occurs even though the sinus cycles following the premature beat are conspicuously prolonged allowing the junctional tissues a longer recovery time. It is suggested that premature atrial excitations which break into the junctional fibers whether they do or do not reach the ventricle may exert a depressing effect upon A-V conduction. This is similar in type to inhibition of the pacemaker function with which it is often associated.

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The prognosis of atrial fibrillation after mitral valvotomy

P B Halmon M D MRCP*

Belfast Northern Ireland

It has been estimated that 20 to 40 per cent of patients who undergo mitral valvotomy will develop atrial fibrillation postoperatively.¹⁻⁴ The persistence of this arrhythmia is of significance since it has a deleterious effect on the circulation and is associated with a high incidence of systemic embolization.

The present study, based on a review of 1 000 mitral valvotomies, was undertaken to assess the prognosis of postoperative atrial fibrillation and study the effect of various factors on its production and abolition.

Material

One thousand mitral valvotomies were performed between 1950 and 1964 in Wards 5 and 6 of the Royal Victoria Hospital Belfast. During the first part of this period the finger or knife was used to divide the mitral valve whereas later a transventricular dilator was used. The surgical technique otherwise remained unchanged.

The cardiac rhythm of 800 patients who survived for a week after their first valvotomy was studied. The rhythm was confirmed by electrocardiogram before and usually more than once after operation. All patients were on digitalis preoperatively. None was given prophylactic quinidine. When quinidine conversion was

required it was attempted on the twelfth postoperative day by giving quinidine sulphate in a dose of 3.6, 9 and 12 grams at 2 hour intervals until conversion was achieved. If required this regimen was repeated on the second and third days. When sinus rhythm was established the patient was started on a maintenance dose of quinidine 3 grams four times a day.

Results

Patients in sinus rhythm preoperatively
Of the 500 patients studied sinus rhythm was present in 620 (72.4 per cent). One hundred and thirty seven (22 per cent) developed atrial fibrillation after the mitral valvotomy. It was found that development of atrial fibrillation was more likely in patients over 40 years of age ($p < 0.001$), in those with a history of paroxysmal attacks of severe palpitations ($p < 0.001$) and in those in whom no or only slight division of commissures was achieved at valvotomy ($0.02 < p < 0.05$). Sex, right ventricular hypertrophy, preoperative mitral regurgitation and the surgeon's estimate of postoperative reflux had no influence on the results.

The onset of atrial fibrillation usually occurred in the first postoperative week and was maximal in the second 24 hours after operation (Fig. 1). The incidence of spontaneous reversion was 13.6 per cent.

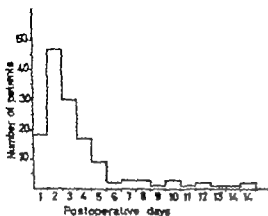


Fig. 1 Time of onset of atrial fibrillation after mitral valvotomy

when atrial fibrillation appeared during the first postoperative week and 18.1 per cent when it appeared later. Spontaneous reversion to sinus rhythm occurred in a total of 18 patients (13.1 per cent). Quinidine conversion was attempted in the other 119 patients and was successful in 84 (70.5 per cent). The attempt at conversion had to be abandoned because of severe gastrointestinal disturbances in 3 patients. Signs of mild toxicity, not requiring discontinuation of therapy, however, were seen in 15 patients. Age, sex, right ventricular hypertrophy and cardiothoracic ratio did not influence spontaneous or quinidine conversion. Quinidine conversion was successful in 23.3 per cent of patients who had mitral regurgitation preoperatively and in 75 per cent when the patients showed no evidence of an incompetent mitral valve. Sinus rhythm was established in 42.8 per cent of patients in whom only poor division of coronary vessels was achieved. The percentage of conversion rose to 74.1 per cent in the group in which mitral obstruction was satisfactorily relieved. The above-mentioned differences just failed to reach statistical significance at the 0.05 level.

Patients in atrial fibrillation preoperatively. There were 235 patients (27.5 per cent) in this group. After mitral valvotomy, quinidine conversion was attempted in 150 patients. Sinus rhythm was established in 6 (4.0 per cent). There was one case of spontaneous conversion among the 235

patients. Reversion to sinus rhythm occurred in this patient 3 weeks after valvotomy, although she has had atrial fibrillation for over 3 years.

Follow up of patients. Of the 18 spontaneous conversions there were 7 reversions to atrial fibrillation after an interval of 1 to 10 years of sinus rhythm. The average duration was 4.7 years. Sinus rhythm persisted up to the present time in 11 patients with an average duration of 3.6 years (Table I).

Follow up data were available in 80 of the 64 patients in whom sinus rhythm was successfully reestablished with quinidine. Reversion to atrial fibrillation occurred in 60 patients after an interval of 1 month to 9 years. The average duration was 2.8 years. Twenty of them are still in sinus rhythm. In these it has been present for 1

Table I Follow up results in 18 patients whose postoperative atrial fibrillation converted to sinus rhythm spontaneously (100 per cent follow up)

	Sinus rhythm period	Reversion to atrial fibrillation
Number of patients	11	7
Longest follow up (yr)	5	10
Average duration of sinus rhythm (yr)	3.6	4.7

Table II Follow up results in 60 patients whose postoperative atrial fibrillation was converted to sinus rhythm with quinidine

	Sinus rhythm period	Reversion to atrial fibrillation
Number of patients	20	40
Longest follow up (yr)	7	9
Average duration of sinus rhythm (yr)	3.4	2.8

Table III Three year follow up of patients with spontaneous and quinidine conversion

	Number of patients	Rhythm	Length of follow up (yr)		
			1	2	3
Spontaneous conversion	15	SR AI	14 1	12 2	12 3
Quinidine conversion (postoperative AI)	47	SR AI	44 3	25 22	17 10
Quinidine conversion (preoperative AI)	6	SR AI	5 1	0 0	0 0

SR = Sinus rhythm; AI = Atrial fibrillation

to 7 years with an average duration of 3.4 years (Table II).

In all 6 patients in whom long standing atrial fibrillation had been abolished postoperatively, reversion to atrial fibrillation occurred within 1 year within 6 months in 5 of them.

When all of the patients who had been followed for at least 3 years were examined the superior prognosis of spontaneous conversion was clearly demonstrated (Table III). In view of the good long term result in the latter group it was compared with the group of patients who maintained sinus rhythm throughout the postoperative period. The corresponding figures in these two groups for patients in sinus rhythm at 1, 2 and 3 years of follow up were 94, 87, 80 and 93, 93, 90 per cent respectively.

Discussion

The incidence of postoperative atrial fibrillation depends to some extent on preoperative preparation. Kittle and Crockett⁴ found that although the overall incidence of postoperative atrial fibrillation was 26 per cent in patients who received quinidine and digoxin preoperatively it was only 16 per cent, 30 to 35 per cent of their patients who were given either drug or none at all developed atrial fibrillation.

The younger the patient the less likely is the development of atrial fibrillation.

Patients over 40 who undergo valvotomy are particularly susceptible to the development of atrial fibrillation and this is the group in which every attempt should be made to prevent this complication by the use of prophylactic drug therapy. A history of previous episodes of severe palpitations is also a good indication for prophylactic therapy.

It has been suggested⁷ that it is more difficult to establish sinus rhythm in patients who had significant mitral obstruction. It seems to be probable that the increased left atrial pressure due to the narrowed valve orifice not only militates against the success of conversion but predisposes to postoperative changes in rhythm. This was confirmed by the finding that patients whose significant mitral obstruction was unrelieved at operation were more likely to develop postoperative fibrillation.

There have been varying reports of the importance of mitral incompetence in the occurrence of postoperative atrial fibrillation. Kittle and Crockett⁴ stated that only 1 of their 41 patients who fibrillated after operation had predominant mitral regurgitation. Others^{8,9} found positive correlation between the presence of mitral incompetence and postoperative fibrillation. The results in this study did not support the latter findings. Postoperative fibrillation was present in 21.7 per cent of patients without and in 27.6 per

cent with mitral insufficiency. Severity of reflux as estimated by the surgeon did not bear a positive correlation with the appearance of atrial fibrillation. The onset of atrial fibrillation appears most commonly during the first postoperative week. Attention has been drawn to the higher incidence of spontaneous conversion when atrial fibrillation occurred during this period.¹¹ Among our patients those developing atrial fibrillation during the second week had a higher rate of spontaneous conversion. The small numbers did not allow statistical analysis. If conversion to sinus rhythm takes place spontaneously, the prognosis is good. Eighty per cent of our patients have remained in sinus rhythm for up to 3 years.

The over all percentage of spontaneous conversion was smaller in the present series than in most other series reported in the literature. A possible reason for this discrepancy is that all patients with recent atrial fibrillation were given quinidine sulfate on the fourteenth postoperative day in an attempt to establish sinus rhythm. In the absence of quinidine therapy in some of these patients spontaneous conversion might have occurred at a later date.

Quinidine conversion was successful in 72.4 per cent. A success rate of 40 per cent was achieved with chronic atrial fibrillation. This compares with figures of 70 to 95 per cent reported in postoperative cases^{11,12} and with 58.5 per cent reported by Esmeijer¹³ in 1058 cases of chronic atrial fibrillation.

There were no embolic episodes during conversion. It is undoubted that this risk exists but its likelihood has been assessed to be not more than 1.5 per cent in the 48 hours after conversion¹ and is likely to be even smaller in postoperative patients in whom the left atrium has been flushed free of clots and the atrial appendage removed. This inherent danger of conversion is more than balanced by the strong evidence for the deleterious effects of continued atrial fibrillation¹⁴ and for the circulatory improvement that follows establishment of sinus rhythm.^{15,16}

The relapse rate among patients requiring quinidine for conversion was disappointingly high. Our results indicate

that it is not worth while to attempt conversion in patients who fibrillated prior to operation since reversion to atrial fibrillation occurred in 83 per cent of them within 6 months.

Patients who require quinidine for post-operative atrial fibrillation will eventually suffer a recurrence of this arrhythmia. However 50 per cent of them were in sinus rhythm after 2 years and 30 per cent after 3 years. Since it is impossible to predict the prognosis of the individual case conversion in every patient seems to be justified. Bloom¹⁶ reported one patient with preoperative atrial fibrillation in whom spontaneous conversion to sinus rhythm occurred after valvotomy. He could find no other documented cases in the literature. We have encountered one such case out of 235 patients. We can only assume that in our case the onset of atrial fibrillation was not caused by severe rheumatic involvement of the myocardium but was initiated and maintained by the high left atrial pressure stretching of the atrial wall and the abnormal hemodynamic situation caused by the tight mitral stenosis. Once these factors were relieved sinus rhythm returned.

Summary

The prognosis of atrial fibrillation occurring after mitral valvotomy has been reviewed.

Six hundred and twenty patients were in sinus rhythm preoperatively. Atrial fibrillation developed in 137 (22 per cent). In 18 (13.1 per cent) of these conversion to sinus rhythm occurred spontaneously, quinidine was successfully used with the same end result in 84 (72.4 per cent).

Conversion of long standing atrial fibrillation was successful in only 40 per cent of cases.

Once sinus rhythm was established those in whom conversion had occurred spontaneously had the best prognosis.

I wish to thank Dr J. F. Partridge for his permission to study these patients who were all under his care.

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Exercise escalator

For electrocardiographic studies in patients with coronary heart disease

S A Talbot Ph D*

Ivan Likar M B B S

W A Harrison Jr Ph D

Baltimore Md

The exercise testers now used for cardiac investigation were designed for various purposes. Treadmills were developed especially for studies of cardio-respiratory function in persons in a fair degree of health. Bicycle ergometers similarly were designed in Europe mainly for research in physiology rather than pathology. The various step tests were indeed intended to differentiate between subjects of uncertain cardiac status at milder levels of exercise. However they were hardly designed for use with the recent techniques of multilead electrocardiographic recording throughout exercise for exercise maintained at a controlled level of tachycardia nor for clinical investigations involving the old and infirm. For the latter purposes all three of the usual methods have certain disadvantages.

In this country step tests are the most widely used. For the present purpose the main difficulties are that the rate of exercise is hard to regulate and that many patients are awkward and unstable in stepping up and down rapidly when hampered by the electrodes and cable needed to record 12 leads in exercise electrocardiography. During rapid intermittent exercise these electrodes are frequently jotted

loose and artefacts appear in the record particularly in patients who are overweight. Furthermore the work performed during step-tests is difficult to express quantitatively chiefly because the effort expended during descent although considerable can not be stated in terms of work done.

Pedaling on a bicycle is a type of leg exercise to which most subjects are unused in this country. Thus subjects are apt to experience excessive fatigue of the lower limbs before the desired challenge to the cardiopulmonary system is obtained. In our experience many patients have found the requisite balance and coordination difficult or impossible. Of 90 subjects selected for the electrocardiographic exercise test on the Lanoov bicycle 9 were unable to pedal effectively even after practice. Unaccustomed types of exercise are performed more or less inefficiently. Thus it is difficult to infer accurately the physiologic load from the recorded work in any particular individual.

Ordinary walking is natural and thus appears to be an ideal type of work for most physiologic studies and particularly exercise electrocardiography. This principle is applied in treadmill exercise. The usual motor-driven machine however has serious

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Address: Dr J H Harrison, Medical School, 23 N. 17th St, Baltimore Md 21205

drawbacks when used for exercising patients suspected of having coronary heart disease. During the test there is real danger of falling, and in an emergency it is not possible to stop the motion rapidly so that an additional technician is required as a catcher. Apprehension induced in some people by the treadmill exercise adds to the patient's discomfort and produces psychological stress that is significantly disturbing in cardiac tests.

In the attempt to overcome these disadvantages we have designed an exercise tester that is especially suited for multilead electrocardiography during the exercise of patients with coronary heart disease. For this we have used the treadmill principle for an escalator to be driven entirely by the patient's own weight and under his control (Fig 1). Such a device has the following advantages: (1) It presents minimal danger to the weak and unsteady for it automatically arrests as soon as

walking stops. (2) It mainly exercises the muscles habitually used by nonathletic people. (3) The pattern of muscular coordination is already well learned so that the effect of training is minimized. The relative immobility of the upper part of the body during steady exercise permits excellent quality multiple lead in exercise electrocardiograms. (4) The rate of work (power) is directly proportional to the speed of stepping. This speed can be regulated by the physician either for constant stepping rate (power) or with cardiostachometer for constant heart rate (effort). Adjustment is made by means of a manual valve controlling a hydraulic load. (5) The mechanics of such a device are simple; calibration does not change and there is no external power requirement. Unlike bicycle ergometers no minimum speed



Fig 1 Exercise escalator showing position of patient during exercise. Dial for weight, speed and work rate are at right.

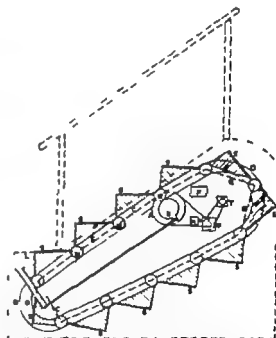


Fig 2 Schematic diagram of exercise escalator. Eleven steps (S) hinge to each other at wheels (H) which are connected to two in a groove between a pair of oval tracks (O). Attached roller chains (C) drive sprockets (A) the shaft of which is connected by belts to an oil pump (P). This pump then circulates oil through a manual needle valve (N) which controls the speed. The tachometer (T) indicates this on a voltmeter (V). A hinged landing (L) actuates a brake (B) when the patient descends to this level. Banisters guard the patient and visible enclosures reduce the perception of height.

need be imposed. Maintenance does not require a specialist.

Design of the exercise escalator

The design of the exercise escalator appears schematically in Fig. 2. This figure shows 11 light wooden 7 inch steps coupled together. These steps rest on a set of ball bearing wheels, each rolling in a groove between a pair of oval tracks. As the steps move down under the patient's weight, roller chains on either side drive a sprocket, the shaft of which is connected by a belt to a hydraulic gear type of pump. This pump circulates oil through a constriction valve which provides the main workload and controls the speed. Speed of walking is sensed by a tachometer which generates a voltage scaled in watts/kilogram meters per minute or steps per minute as desired. A scaling factor which is the patient's weight is preset by a direct reading potentiometer knob. Two ranges are provided on the meter: 0 to 150 and 0 to 300 watts (900 to 1800 kg M/min).

A number of engineering problems were encountered: minimizing the number of wheels and tracks; optimal design of tracks for minimal friction and momentum discontinuity; and lightening the moving mass. We were especially anxious to provide an automatic subject actuated stopping device. This was effected by a set of steel fingers which form the lower landing and actuate a safety brake.

The physical principle is simple. The

work is measured simply by counting steps of known height per minute and multiplying by the subject's weight. This work, done mainly against gravity, is dissipated into various frictional sinks including the needle valve.

We have used the escalator for nearly maximal exercise in 32 normal subjects and to provide controlled cardiac loads in 14 patients with coronary heart disease. All of the subjects were accustomed to climbing steps and no mishaps occurred. The multiple lead electrocardiograms, recorded at frequent intervals during the period of exercise, were remarkably free of muscle noise and base line drift. In contrast, during the two-step test, numerous artefacts on our multiple lead electrocardiograms were produced by excessive body motion and awkwardness in some of these subjects, especially when exercising to a high level of tachycardia.

The escalator has certain disadvantages. It is bulky, with a landing 20 inches above the floor, because one must allow for the return path of the steps. A more compact design would be more complex. Although basically simple, the escalator involves considerable machining and assembly of high quality components so that it is no cheaper to build than a good bicycle ergometer.

We wish to express our gratitude to Mr. A. Fabula, Chief Engineer of the Escalator Division of Otis Corporation, who contributed to the design principles. Mr. John Kummell was responsible for much of the detailed design, drawings and solution of problems of assembly.

Experimental and laboratory reports

Hemodynamic effects of two beta-adrenergic blocking drugs in anesthetized intact dogs

John F. Murray MD*

Edgardo Escobar MD**

Norman L. Jones MD***

Elliot Rapaport MD****

San Francisco Calif

Drugs which block beta receptors of the sympathetic nervous system are assuming importance as potential therapeutic agents and as tools for physiologic investigation. Koch-Weser¹ recently emphasized that ideally drugs used to block beta receptors should do so without significantly stimulating or depressing the heart by direct action. The first beta blocking drug available (3,4-dichloroisoproterenol) abolished the cardiac effects of sympathetic nerve stimulation but exerted sympathomimetic effects of its own. Our purpose was to study in anesthetized dogs the hemodynamic responses that follow the administration of two new beta receptor blocking drugs that are purported to be more specific in their actions. The results show that Nethalide (1-(2-naphthyl)-1,2-isopropylaminoethanol hydrochloride) produces important changes in addition to its adrenergic blocking effects and that propranolol (1-isopropylamino-3-(1-naphthoxy)-2-propanol hydro-

chloride) causes responses which are consistent with the concept of beta blockade but through an unknown mechanism of action.

Methods

Studies were performed on 14 mongrel dogs that weighed between 13.2 and 20.5 kilograms and were anesthetized with intravenous chloralose and urethane (70 and 350 mg per kilogram respectively). A cannula was placed in the brachial artery for sampling blood and was connected to a strain gauge (Statham P 236G) to record pressure. Intrapleural pressure was measured by a mushroom catheter inserted into the right pleural space through a stab wound and connected to a Statham differential manometer (PM131C). The animals were ventilated with a Harvard respirator through a cuffed endotracheal tube at a minute ventilation sufficient to maintain arterial carbon dioxide tension (P_{aCO_2}) within 8 mm Hg of initial values.

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Assoc. (Postgraduate) Medical and Physiological Society (C.M.P.S.) at Los Angeles, Calif. Cardiac Research Research Institute, University of California, San Francisco Medical Center, San Francisco, Calif. Address: Department of Medicine, University of California School of Medicine, Los Angeles, Calif. 90024.

Internist and Postgraduate Fellow of the United States Public Health Service, Present address: Department of Pathophysiology, School of Medicine, University of Chile, Santiago, Chile.

Internist and Postgraduate Fellow of the United States Public Health Service, Present address: Department of Medicine, Postgraduate Medical School of London, London W12 8PL, England.

Assistant Professor of Medicine, University of California, San Francisco Medical Center, San Francisco, Calif.

At intervals throughout the experiment the dog's lungs were inflated to a pressure of approximately 30 mm Hg in order to prevent atelectasis.

Under fluoroscopic guidance a No. 4F catheter with a rapidly responding bead thermometer at its tip* was placed immediately proximal to the aortic valve by retrograde catheterization from a femoral artery to record aortic blood temperature. Similarly a No. 7F or 8F catheter with a closed end and multiple side holes was positioned in the left ventricle; this catheter was used to inject 3 or 4 ml of cooled normal saline rapidly into the left ventricle or to measure left ventricular pressure when connected to a Statham F23gb strain gauge zero level was 6 cm above the base of the animal board. Heart rate was monitored with an electrocardiogram. Cardiac output was measured by the indicator dilution technique with indocyanine green. The left ventricular catheter was preloaded with dye which was rapidly injected while arterial blood was aspirated through a Colson densitometer by a Harvard constant speed withdrawal pump. Standard solutions of dye for calibration were made in the animal's own blood at the end of the experiment. Pressure measurements, indicator dilution and thermomodulation records were obtained with an Electronics for Medicine PR 7 recorder.

A 15 minute adjustment interval was allowed after the preliminary procedures were completed. The control and experimental periods each lasted about 10 minutes during this time we measured cardiac output obtained 9 to 12 aortic thermomodulation recordings made a second measurement of cardiac output and midway in the period recorded left ventricular end diastolic pressure, intrapleural pressure and brachial arterial pressure. Arterial blood was collected to measure P_{aO_2} , P_{aO} , pH and hematocrit ratio. Left ventricular end diastolic transmural pressure was calculated by subtracting mean intrapleural pressure from left ventricular end diastolic pressure measurements were obtained simultaneously during a complete respiratory cycle.

Mean values are reported for two cardiac

output determinations and multiple thermomodulation and heart rate recordings. The paired measurements of cardiac output made during control periods differed from mean values by ± 5.9 per cent. Left ventricular stroke volume (SV) was computed from the mean cardiac output and heart rate (HR) determinations obtained during each experimental period. End diastolic volume (EDV) and end systolic volume (ESV) were derived from the formulas

$$EDV \text{ (ml)} = \frac{SV}{1/k} \quad (1)$$

$$ESV \text{ (ml)} = EDV - SV \quad (2)$$

where k = the average ratio of change in temperature of a beat to that of the preceding beat obtained from successive steps of the aortic thermomodulation curve. Details of the thermomodulation technique have been published.²

Systemic vascular resistance in arbitrary units was calculated by dividing mean arterial pressure (millimeters of mercury) by cardiac output (liters per minute per kilogram). Stroke work index (grams centimeter per kilogram) was calculated by multiplying mean brachial arterial pressure (centimeters of water) minus left ventricular end diastolic pressure (centimeters of water) times SV (milliliters per kilogram).

Mean circumferential shortening rate (MCSR) can be defined as the average velocity of fiber shortening along the inner circumference of the ventricular chamber assuming a spherical ventricle at end systole and end diastole.³

$$MCSR \text{ (cm/sec)} = \frac{2\pi(ed - es)}{sep} \quad (3)$$

where ed = end diastolic radius in centimeters, es = end systolic radius in centimeters and sep = systolic ejection period in seconds obtained from the brachial arterial pressure recording.

End systolic force was calculated as proposed by Holt⁴ from end-systolic circumference and tension derived at end systole* by the Laplace equation

$$Ed \text{ (th)} = \frac{w \text{ (ml)} \times hf \text{ (mm)} \times d \text{ (cm)}}{100 \times \pi \times r \text{ (cm)}} \\ \text{If } k \text{ (mod)} \text{ back over } 1 \text{ the } th \text{ (d)} \text{ (cm)} \text{ (cm)}$$

* by E. G. Green & Corp. Springfield, N. J.

$$T_{\text{mean}} (\text{Gm/cm}) = L_{\text{LVSI}} (\text{Gm/cm}^2) \times r_{\text{es}} (\text{cm})/2 \quad (4)$$

$$T_{\text{out}} (\text{Gm}) = T_{\text{mean}} (\text{Gm/cm}) \times 2 \pi r_{\text{es}} (\text{cm}) \quad (5)$$

End systolic force and or MCSR could not be derived once after propranolol (Dog 14 5 minutes) and twice after Nethalide (Dog 3 5 and 20 minutes) because damping of the arterial pressure record precluded accurate measurement of LVESP and aep.

After control measurements were performed 7 of the animals were given Nethalide and 7 were given propranolol. Nethalide 50 mg per kilogram diluted to 100 ml in dextrose and water was administered intravenously over a 15 minute period. Propranolol 0.5 mg per kilogram diluted to 30 ml in saline was infused in 5 minutes. All hemodynamic measurements were repeated at the completion of the infusion of the drugs and 15 minutes later. Since the determinations took 10 minutes to perform these are called the 5 minute and the 20 minute postdrug periods. Subsequently to test the adequacy of beta-adrenergic blockade brachial arterial pressure and HR were recorded after the intravenous injection of 10 μ g of isoproterenol in 2 minutes the injection was continued and a single cardiac output 3 to 4 thermal curves and pressures were recorded rapidly after a total of 20 μ g had been given. In most dogs all observations were then repeated 10 minutes after the intravenous administration of 5 mg of atropine (total). The extent of neurogenic blockade was further evaluated by the responses of brachial arterial pressure and HR to bilateral carotid arterial occlusion during the control period after the 20 minute postdrug period and after atropine was injected.

Statistical techniques were used to evaluate two aspects of the study: (1) the effect of each drug examined separately on the variables under consideration and (2) a quantitative comparison of the two drugs. The first of these was analyzed by using each animal as its own control and the null hypothesis was that the mean difference between control and drug periods was zero. To compare the effects of one drug with the other the difference in each variable between control and drug periods

in a given animal was treated as the datum and a comparison was made between mean data for the two drugs; the null hypothesis was that there was no difference between the means.⁴

Results

Data from the 14 experiments are shown in Table I (for Nethalide) and Table II (for propranolol). Dogs No 7 and 14 were not included in the statistical analysis presented in Table III but are discussed separately because of the difficulty encountered in anesthetizing these animals which affected control values. The mean values of all hemodynamic parameters measured or derived did not differ statistically between the two groups during the control periods.

Hemodynamic effects. Mean cardiac output rose nearly 60 per cent above control values in dogs that received Nethalide ($p < 0.001$) and did not change significantly in those given propranolol. The rise in cardiac output in dogs receiving Nethalide was the result of an increase in both HR and SV. Although there was a tendency for the values to return toward control values 20 minutes after beta-blocking drugs were given the magnitude of the changes in cardiac output and HR responses was still significantly different between drugs.

The ESV/EDV ratio decreased in dogs given Nethalide and increased in those that received propranolol. The changes are significant at 5 and 20 minutes in the animals receiving propranolol and at 5 minutes in the dogs given Nethalide. Differences between the two drugs are significant during both the 5 minute and 20 minute postdrug periods. Neither drug caused significant changes in heart size but since they had opposite influences on ESV and EDV there are significant differences between the two drugs when compared at 5 minutes (ESV) and 20 minutes (ESV and EDV).

Left ventricular transmural pressure rose above control values 5 minutes after propranolol was given but was not affected

Table 11 *Ureodynamia data after the administration of propenoal (0 mg/kg IV in 5 min)*

Dose g	Q (ml/min/kg)	HR (beats/min)	V _I (ml/kg)	$F^{N1}/ED1$ ()	F^{D1} (ml/kg)	F^{N1} (ml/kg)	17 (mm Hg)	$F^{17}/H1$ (mm Hg)	SVR (mm Hg)	SVI (Cm V/kg)
8 C	161	90	1.82	41.6	4.00	2.18	155	11.4	942	3.48
5	169	103	1.61	99.8	4.07	2.43	174	17.9	1031	3.46
20	165	96	1.72	39.4	4.21	2.51	162	14.6	945	3.45
9 C	217	100	2.17	58.2	5.18	3.02	143	15.4	657	3.76
5	203	121	1.99	64.8	4.81	3.12	145	16.4	708	2.94
20	201	106	1.98	61.3	4.97	2.98	149	18.1	681	3.09
10 C	261	170	2.17	65.4	6.28	4.11	171	17.7	656	4.32
5	201	135	1.91	75.9	6.25	4.74	171	25.4	899	2.99
20	202	136	1.49	76.1	6.37	4.78	174	19.0	970	1.14
11 C	158	106	1.46	64.4	4.11	2.65	149	11.0	911	2.74
5	152	115	1.79	60.1	4.20	2.91	151	13.6	993	2.41
20	158	120	1.32	63.6	4.70	2.68	151	12.6	954	2.48
12 C	207	135	1.90	73.8	5.72	4.21	152	16.1	648	2.36
5	217	118	1.64	75.9	7.41	5.80	156	19.9	626	2.91
20	225	117	1.92	71.4	7.79	5.87	140	17.9	623	3.19
13 C	182	121	1.48	46.0	3.56	2.09	131	11.1	721	2.17
5	167	106	1.57	94.9	1.64	2.07	158	4.1	329	2.43
20	175	109	1.61	70.0	5.19	3.58	144	22.7	821	2.66
14 C	501	149	2.91	52.4	4.79	2.77	156	22.9	619	4.59
5	935	135	1.72	48.4	4.15	2.42	177	45.2	691	4.5
20	253	138	1.85	71.4	5.18	3.34	178	34.1	698	3.62
Vic A (Dose 8.13)										
C	197	113	1.77	67.5	4.91	3.01	137	14.5	61	3.21
5	155	117	1.99	67.1	5.10	1.51	151	19.6	919	2.86
20	148	114	1.66	68.1	5.41	1.77	152	17.5	821	3.00

1 kg 1.45 g 200 four 1 T M 1

Table III Statistical comparisons of results in 12 animals receiving either Nethalide (N) or propranolol (P)*

	Drug + 5 min			Drug + 20 min		
	Δ (C-5 min)	SE V	p	Δ (C-20 min)	SE V	p
Q (ml/min/kg)						
N	109	15.1	<0.001	54	13.4	<0.075
P	-17	10.0	>0.20	-9	10.9	>0.40
Δ (N-P)	126	18.1	<0.001	63	17.3	<0.005
HR (beats/min)						
N	34	7.6	<0.01	26	6.2	<0.01
P	4	6.9	>0.50	2	5.8	>0.50
Δ (N-P)	30	10.2	<0.075	24	8.5	<0.025
SV (ml/kg)						
N	0.24	0.03	<0.001	-0.04	0.09	>0.50
P	-0.18	0.15	>0.20	-0.11	0.15	>0.50
Δ (N-P)	0.42	0.15	<0.075	0.07	0.18	>0.50
ESV/EDV (%)						
N	-4.8	1.3	<0.075	-2.2	1.2	>0.10
P	4.6	1.7	<0.05	5.8	1.6	<0.05
Δ (N-P)	-9.4	2.1	<0.005	-8.0	2.0	<0.005
LVTMP						
N	0.3	2.0	>0.20	-3.3	1.4	>0.05
P	5.1	1.5	<0.075	3.1	1.3	>0.05
Δ (N-P)	-4.8	2.5	>0.05	-6.4	1.9	<0.01
AP (mm Hg)						
N	-12	8.4	>0.20	0	6.9	>0.50
P	6	3.0	>0.10	5	7.4	>0.05
Δ (N-P)	-18	8.9	>0.05	-5	7.3	>0.50
SVR† (units)						
N	-309	33	<0.001	-156	33	<0.01
P	17	28	<0.05	59	33	>0.10
Δ (N-P)	-386	44	<0.001	-215	47	<0.005

*D at 5, 7 and 11 min or 1 d d

†SVR (mean) = mean AP (mm Hg)/Q (L/min/kg)

P is to be able to see the first test to T file

Δ (N-P) Probable value of comparison between N and P. The S-test at 5, 20-min or both are compared with control data (C).

by the administration of Nethalide. All the changes encountered were due to variations in left ventricular end-diastolic pressure, intrapleural pressure remained constant. Significant differences between drugs were apparent in left ventricular transmural pressure at 20 minutes. Although the drugs had variable effects on brachial arterial pressure, Nethalide caused a significant decrease and propranolol an increase in systemic vascular resistance. No significant change occurred in stroke work index.

End systolic force and end systolic circumference. A significant correlation between end systolic force and end systolic circumference ($r = 0.83$, $p < 0.01$) was found for the control data (Fig. 1). Twelve

End systolic force and end systolic circumference. A significant correlation between end systolic force and end systolic circumference ($r = 0.83$, $p < 0.01$) was found for the control data (Fig. 1). Twelve

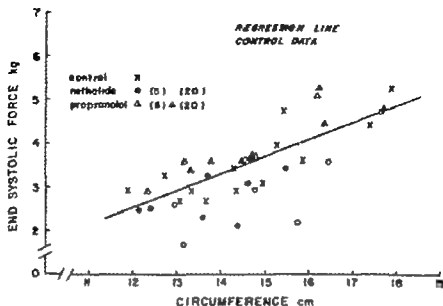


Fig. 1 Relationship between end systolic force and end systolic circumference during control periods and after the administration of Nethalide and propranolol

of the thirteen values for end systolic force and end systolic circumference obtained under the influence of propranolol lie above the regression line for the control periods ($p < 0.001$ by sign test) all but one of the twelve results from the Nethalide experiments are below the control regression line ($p < 0.001$ by sign test). Comparison between force values after administration of both drugs and control measurements reveals that Nethalide caused a decrease ($p < 0.001$) and propranolol an increase ($p < 0.01$) in end systolic force.

Mean circumferential shortening rate and end diastolic volume. There is a significant inverse relationship between mean circumferential shortening rate and EDV ($r = -0.55$, $p < 0.05$) during the control periods (Fig. 2). After infusion of Nethalide more points are above than below the regression line for the control data but the scatter is very wide. All of the values from the propranolol experiments however are below the control regression line ($p < 0.001$ by sign test). Comparison between shortening velocity values after administration of both drugs and control measurements reveals that Nethalide did not change ($p > 0.20$) and that propranolol decreased mean circumferential shortening rate ($p < 0.001$).

Mean circumferential shortening rate and end systolic force. The relationship between mean circumferential shortening rate and end systolic force during control periods approaches significance ($0.05 < p < 0.10$) (Fig. 3). After the administration of Nethalide data are equally above and below the control regression line however all but two of the values from the propranolol experiments lie below the line ($p < 0.01$).

Responses to isoproterenol. The infusion of 10 μ g of isoproterenol produced virtually no change in HR, systolic diastolic and mean brachial arterial pressures or systolic ejection period. Although isoproterenol was not given to these dogs before the administration of blocking drugs 10 μ g causes tachycardia, widens pulse pressure and increases contraction velocity in normal animals.⁸ Twenty micrograms of isoproterenol produced significant changes in ESV/EDV and systemic vascular resistance (Nethalide group) and cardiac output and stroke volume (propranolol group); these indicate that partial breakthrough of the blockade had occurred at the time isoproterenol was given although inhibition was probably more complete at an earlier time.

Responses to atropine. After the effects of

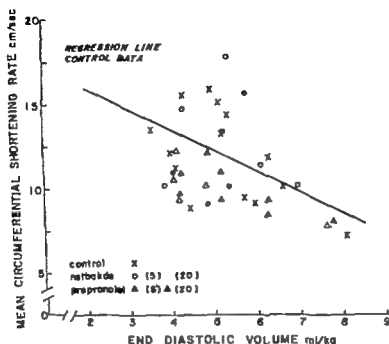


Fig 2 Relationship between mean circumferential shortening rate (MCSR) and end-diastolic volume (EDV) during control periods and after the administration of Nethalide and propranolol

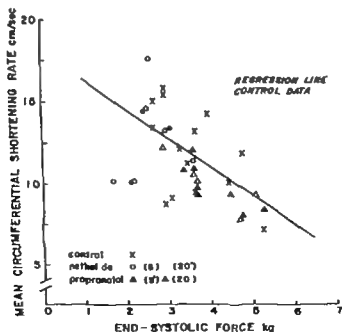


Fig 3 Relationship between mean circumferential shortening rate (MCSR) and end systolic force during control periods and after the administration of Nethalide and propranolol

isoproterenol were dissipated atropine was given in order to study the effects of combined beta adrenergic and cholinergic blockade. The only significant change that followed atropine in dogs which had received Nethalide was a fall in left ventricular end diastolic pressure. In dogs that received propranolol atropine had a more noticeable effect causing significant changes in SV, EDA and systemic vascular resistance.

Carotid occlusion. The main responses to bilateral carotid occlusion during control periods were increases in HR of 31 beats per minute and in arterial pressure of 53 mm Hg. These responses were significantly reduced after both Nethalide and propranolol—a rise of 7 beats per minute and 26 mm Hg and a rise of 16 beats per minute and 35 mm Hg respectively.

Duration of action. With few exceptions the hemodynamic changes that followed infusion of both drugs were maximal 5 minutes after administration. When the 5 minute and 20 minute intervals are compared in the Nethalide experiments significantly different results were obtained during the later period always toward control values in cardiac output, SV, EDA ratio, mean brachial arterial pressure and systemic vascular resistance. No significant difference in any parameter was found between the 5 minute and 20 minute periods after propranolol.

Dogs 7 and 14. One dog that received Nethalide (Dog No 7) and one that was given propranolol (Dog No 14) were not included in the statistical analyses presented in Table III. Dog No 7 was difficult to anesthetize and had an extremely high cardiac output that diminished during the course of the experiment (Table I). It is uncertain whether the decline represents a drug effect or spontaneous with drawal of stimuli occasioned by the traumatic anesthesia. Since the changes in cardiac output, HR and SV were in general opposite to those in the other animals that received Nethalide the elimination of Dog No 7 from consideration influences the statistical results. Dog No 14 also had an elevated initial cardiac output and extremely high brachial arterial and left ventricular end diastolic pressures (Table II) when this dog was

given propranolol. brachial arterial pressure and cardiac output fell slightly but remained well above usual control values and left ventricular transmural pressure rose to 55 mm Hg. Since the changes in Dog No 14 were qualitatively similar to those in the remainder of the dogs that received propranolol its exclusion does not greatly affect the statistical analysis of that group.

Other studies. No changes occurred in Pa, Pac, pHi or arterial hematocrit that could be attributed to the effects of either drug. On a few occasions premature ventricular contractions appeared during the administration of Nethalide these could be increased in frequency or made to disappear by changing the rate of infusion. In 4 dogs an erythematous flush became apparent in shaved areas while Nethalide was being given and persisted for the remainder of the experiment. The flush had the appearance of extreme vasodilatation and was coincident with hemodynamic evidence of high cardiac output and a decrease in brachial arterial pressure and systemic vascular resistance.

Discussion

Nethalide was described by Black and Stephenson¹ as an effective antagonist of beta adrenergic receptors and relative free from intrinsic sympathomimetic activity. Recently the results of several investigations show that Nethalide produces a variety of pharmacologic effects in addition to its beta receptor inhibition.²⁻¹⁰ Our data demonstrate that in addition to its beta blocking action Nethalide affects both the heart and peripheral blood vessels.

Cardiac output increased above control levels after the administration of Nethalide because of a rise in both SV and HR. Donald Kvale and Shepherd² also noted an increase in cardiac output and SV after Nethalide (6 mg per kilogram) but the HR response was variable. They studied 4 unanesthetized dogs with denervated hearts and observed an increase in HR which indicates that Nethalide has direct stimulating actions on the heart. Koch Weser³ also found that Nethalide had a weakly positive chronotropic effect on isolated cat atrial tissue. An additional

mechanism by which the HR may increase in response to Nethalide despite blockade of sympathetic stimuli is through inhibition of the parasympathetic nervous system as demonstrated by Ledsonne and associates.⁹ Blockade of peripheral vagal activity was shown by James and Naderu¹⁰ by direct perfusion of the sinus node with Nethalide. The failure of atropine to significantly increase HR in our experiments also suggests that Nethalide had blocked vagal activity prior to the administration of atropine. The relative contribution of these mechanisms to the observed increase in HR is unknown and the role of each may vary in different experimental conditions.

Calculated systemic resistance decreased significantly in this study after Nethalide was infused and since arterial pressure tended to fall despite an increase in cardiac output it can be inferred that vasodilatation had occurred. A similar conclusion was reported by Black and Stephenson⁷ and led to a trial of Nethalide as a hypotensive agent.¹¹ Vasodilatation probably caused the conspicuous flush noted in some animals and has been documented in studies of peripheral blood flow by Lowe and Robinson.¹ This is most likely a non-adrenergic effect of the drug since blockade of beta sympathetic activity in peripheral vessels should cause arterial constriction and venodilatation.¹²

The mechanisms by which Nethalide influences cardiac output are complex and could include effects of the drug on factors such as initial myocardial fiber length, contractile performance and afterload which are difficult to define separately. We have considered that the equivalent in the intact animal to afterload as studied in isolated papillary muscle preparations is end systolic force and that mean circumferential shortening rate is a reflection of isotropic responsiveness. Mean circumferential shortening rate after Nethalide was not significantly different from control values and the relationship between shortening velocity and both end systolic force and end diastolic volume was also normal by these criteria; the drug does not affect the contractile state of the myocardium. A negative inotropic effect is suggested however by the in-

fluence of the drug on the end systolic force per unit of end systolic circumference. A reduction in afterload by a peripheral mechanism (e.g. arterial vasodilatation) should result in the development of less end systolic force but at a dimension defined by the normal force to end systolic circumference relationship (Fig. 1) since all of the values obtained after Nethalide lie below the regression line for the control data a negative inotropic influence is inferred because less force is generated per unit of circumference. A negative inotropic effect is not incompatible with the findings that the ESD/EDV ratio decreased and stroke volume and cardiac output increased. These results indicate that the preponderant effect of the drug is vasodilatation and that enhanced ventricular emptying occurred secondary to the fall in afterload despite a negative inotropic effect. No consistent variation occurred in either stroke work index or EDV that would implicate the Frank-Starling mechanism in the hemodynamic events after Nethalide.

Propranolol a newer beta blocking drug has superseded Nethalide for clinical studies because it has fewer unpleasant side effects when given to patients. Unlike Nethalide it apparently does not have a carcinogenic effect in mice.¹³ The original report by Black and associates¹⁴ claimed that propranolol had essentially the same pharmacologic properties as Nethalide and was 10 times as potent. A dose of 0.5 mg per kilogram was used in the present investigation because it is one tenth of the amount of Nethalide given and because this quantity has been shown to abolish the heart rate response of dogs to sympathetic nerve stimulation.⁹ Contrary to previous reports data from the present study demonstrate that the two drugs cause different hemodynamic changes when given in a 10:1 ratio to unanesthetized intact dogs.

Propranolol did not change cardiac output, HR or SV but raised the ESD/EDV ratio and left ventricular end diastolic pressure. All animals given propranolol showed an increase in left ventricular transmural pressure associated with variable changes in EDV; this is best explained by a decrease in diastolic distensibility.

of the ventricle although we have not eliminated the possibility that intrapericardial pressure increased. It is possible that this alteration is due to the effects of adrenergic blockade on the ventricular myocardium which would be consistent with the observation by Helfner and associates¹⁶ that epinephrine α beta receptor stimulator increased diastolic distensibility. Mitchell, Linden, and Sarnoff¹⁷ however found that adrenergic activity did not change the pressure fiber length characteristics of the ventricle. An alternative explanation is that the drug exerts a direct effect on the mechanical properties of heart muscle by decreasing the compliance of either the contractile or parallel elastic elements.

Mean circumferential shortening rate is a function of end systolic force (which includes in part total peripheral resistance) EDV and the contractile state of the myocardium. The administration of propranolol caused a significant increase in end systolic force which by itself should reduce shortening velocity as defined by the normal force velocity relationship (regression line in Fig. 3). Virtually all of the values after the drug were lower than expected which could be accounted for by either a decreased EDV or a negative inotropic effect. Since mean circumferential shortening rate was also lower than normal at any given EDV (Fig. 2) propranolol must have had a negative inotropic influence.

The evidence favoring a negative inotropic response to the drug occurred while there was a heightened end systolic force at any end systolic circumference. The alteration in force derived by multiplying end systolic tension and end systolic circumference is due to changes in tension because variations in circumference alone would not deviate from the expected force circumference relationship (Fig. 1). Two factors contribute to end systolic muscle tension: an active component dependent on the intensity of muscle fiber contraction and a passive component determined by the elasticity of the muscle (series elastic element). An increase in either would augment end systolic tension. We cannot distinguish between these two with certainty but in view of the evidence

which favors a negative inotropic effect of the drug, and the unlikely possibility of recruitment of more muscle fibers, a decreased compliance of the series elastic element is more probable. It is possible therefore that propranolol affects both series and parallel elastic elements throughout the cardiac cycle.

Our data apply only to the effects of Nethalide and propranolol in intact dogs anesthetized with chloralose urethane. The degree of sympathetic stimulation in these animals was variable and in some instances (Dogs No. 7 and 14) was presumably high. It can be inferred that sympathetic activity was not inordinate during the control periods in most dogs given propranolol because after beta adrenergic blockade there was no decrease in heart rate and only contractility and elasticity were affected. It is conceivable that different thresholds exist at which propranolol influences various modalities of beta receptor activity; however the responses could also be due to a direct effect of the drug on the heart and our data are insufficient to distinguish between these possibilities.

Summary

The hemodynamic effects of two beta blocking drugs were evaluated in intact dogs anesthetized with chloralose urethane. Nethalide (5 mg per kilogram intravenously in 15 minutes) significantly increased cardiac output, heart rate, and stroke volume and decreased end systolic volume/end diastolic volume ratio and systemic vascular resistance. The decrease in calculated end systolic force per unit of end systolic circumference suggests a negative inotropic effect. The preponderant effect of the drug was arterial dilatation which cannot be explained by beta adrenergic blockade. Better ventricular emptying was probably secondary to decreased afterload since end diastolic volume did not change.

The chief rate of activity of propranolol (0.5 mg per kilogram intravenously in 5 minutes) was on the myocardium. Left ventricular end diastolic pressure increased without a change in end diastolic volume, which indicates that diastolic distensibility was reduced. In addition, mean circum-

ferential shortening velocity decreased which suggests a negative inotropic effect and diastolic volume and stroke work were unchanged and end systolic force per unit of end systolic circumference increased. The latter is perhaps due to an increased contribution of elasticity to end systolic tension. We do not know whether these results are due to inhibition of beta adrenergic activity or to direct effects on the myocardium.

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Chronic pharmacologic treatment of experimental hypoxic pulmonary hypertension

With observations on rate of change in pulmonary arterial pressure

John H. A. Vogel M.D.*

Daniel Cameron*

Gail Jamieson B.A.***

Denver, Colo.

Previous reports from this laboratory have shown that ligation of the left pulmonary artery in the newborn calf results in progressive pulmonary hypertension when performed at an altitude of 5000 feet¹ but not at sea level; thus a preparation is produced for the study of hypoxic pulmonary hypertension. In this paper a detailed evaluation of chronic pharmacologic therapy in such a preparation is reported and contrasted with acute treatment.

Methods

Ligation of the left pulmonary artery was performed in a newborn calf within 24 hours of birth. The animal was premedicated with 0.4 mg of atropine subcutaneously. A plastic bag was placed over its head and induction was accomplished with a high flow rate of 4 per cent halothane² and 4 liters per minute of both oxygen and nitrous oxide. Within 4 minutes it was possible to intubate the animal

after which the animal was maintained with a 10.5 per cent concentration of halothane. After the chest had been opened it was possible to maintain the animal with 250 c.c. of both nitrous oxide and oxygen without halothane. Upon completion of the surgical procedure, the animal was awake within 5 minutes. The animal was then promptly returned to the Research Farm. The mother's colostrum and 50 c.c. of anti-coli enteritidis *Pasteurella* serum³ were given to the animal.

Serial right heart catheterizations were performed percutaneously via an external jugular vein with either a PE 60 tubing or a No. 6F smooth bore catheter. Systemic arterial blood and pressures were obtained by needle puncture of the descending aorta through the last intercostal space on the left using a 6 inch 18 gauge thin walled needle. All studies were performed with the animal standing erect in a strachion without premedication.¹

Five months after surgery, the animal

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*Assistant Professor of Medicine and Associate Director, Cardiac Catheterization Laboratory, University of Colorado Medical Center, Denver, Colo. Present address: Medical Center, University of Illinois Medical Center, 4200 East North Ave., Chicago, Ill. 60640.

***Superior of Animal Chamber Research Farm, University of Colorado Medical Center. Research Associate, Cardiovascular Laboratory, University of Colorado Medical Center. (Currently employed as Phlebotomist by Ayerst Laboratories, New York, N.Y.)

Harvard Lockhart Laboratories, Kansas City, Mo.

was started on a program of daily intravenous acetylcholine* and nasal oxygen 5 to 10 liters per minute. This program was continued for 13 days. The acetylcholine was administered in a continuous manner using a micro-flow Sage pump† which was taped to the animal's head. After treatment was discontinued serial observations of pulmonary arterial pressure were obtained over a 7 week period. The calf was then placed in a 1 ton van and transported to sea level (Houston Texas). This trip required 25 hours. Right heart catheterization was performed at 1, 16 and 40 hours and 1 week and 4 months after arrival at sea level. Serial electrocardiograms were also obtained.

Pressures were obtained using a F23db Statham strain gauge energized by an Electronics for Medicine amplifier and recorded on an Electronics for Medicine photographic recorder. Mean pressures were obtained electronically. The oxygen content and capacity of samples of blood were obtained by the method of Van Slyke and Neil. Blood pH was determined by the micro technique of Siggaard Andersen and associates‡ and oxygen and carbon dioxide tensions were measured directly with electrodes at body temperature using the Radiometer§ apparatus. Carbon-dioxide tension was checked by the Astrup microtometer technique‡ as well as by the Van Slyke method using the chart of Scudron.

Results

Two weeks after surgery mean pulmonary arterial pressure was 33 mm Hg which is in the normal range for a 2 week old calf. As shown in Fig. 1 and Table I there was a progressive rise in mean pulmonary arterial pressure from 33 mm Hg at 2 months to 120 mm Hg at 3 months. This was associated with a decrease in cardiac output as evidenced by widening of the arteriovenous oxygen difference to 7.22 volumes per cent from 5.56. P_{aO_2} was essentially unchanged being 59.0 mm Hg. The response of the calf to various combinations of acetylcholine and oxygen was

then determined as shown in Fig. 2. With the administration of 44 per cent oxygen by mask resulting in a P_{aO_2} of 114.8 mm Hg mean pulmonary arterial pressure was reduced from 126 to 95 mm Hg. It returned promptly to control levels after the discontinuation of oxygen. With an infusion of acetylcholine at a rate of 4 mg per minute over a 3 minute period mean pulmonary arterial pressure was reduced from 120 to 75 mm Hg whereas aortic pressure decreased slightly from 120 to 105 mm Hg. Five minutes after discontinuation of acetylcholine pulmonary arterial pressure had returned to control levels. Acetylcholine was then readministered in a dose of 1.5 mg per minute over a 17 minute period. This resulted in a decrease in mean pulmonary arterial pressure from 122 to 80 mm Hg and in mean aortic pressure to 115 mm Hg. Mean pulmonary arterial pressure then rose slowly being 100 mm Hg at 1 minute after acetylcholine was discontinued and 109 mm Hg an hour later. The administration of 100 mg of tolazoline into the pulmonary artery was without effect on pulmonary arterial pressure (not shown on the chart).

Acetylcholine was then administered at a rate of 1 mg per minute over a 90-minute period. Mean pulmonary arterial pressure was reduced from 109 to 90 mm Hg. Of interest is the fact that 30 minutes after acetylcholine was discontinued mean pulmonary arterial pressure had remained unchanged at 90 mm Hg with readministration of acetylcholine in a dose of 10 mg per minute mean pulmonary arterial pressure was reduced to 60 mm Hg and with the addition of nasal oxygen at 10 liters per minute to 5 mm Hg. When acetylcholine was discontinued mean pulmonary arterial pressure rose to 100 mm Hg and with discontinuation of oxygen there was a prompt rise to 107 mm Hg. Forty five minutes later acetylcholine and oxygen again effected a fall in mean pulmonary arterial pressure from 107 to 55 mm Hg which was associated with little change in mean aortic pressure from 107 to 10 mm Hg.

Subsequently acetylcholine and oxygen were given intermittently for 17 additional days. In Table II the acetylcholine and oxygen treatment is detailed over this

*Kindly supplied by Marsh and Co.
†Model 12, P-I strain 14, WPI, Inc., N.Y.
‡Radiometer, Copenhagen, Denmark.

Manufacturing

Cult No.	Treatments	Mean fresh mass (mm Hg)				O vol ()		C	I	J	pH	pH	H ₂ O (mm)	H ₂ O rate
		11 deg				S	O							
		R	J	I	11 deg									
1	Re 1 (2 wk old)	4	33	114	14	61.6	92.7	5.56	69.2	7.119	7.111	15.9	100	
2	Re 2 (2 wk old)	3	30	145	57.9	99.4	5.45	40.8	39.7	7.191	7.154	11.6	100	
3	1 min in 1 N ₂	75	31	31	47.0	80.1	6.00	50.8	39.1	4.08	7.161	11.2	100	
4	2 min 13 per cent O ₂ (m.l.)	90	90	1.0	21	54	96.5	5.56	61.0	7.441	7.390	11.6	100	
5	3 min 13 per cent O ₂ (m.l.)	145	109	14	38.2	61.9	5.31	115.8	41.9	7.452	7.410	11.3	100	
6	4 min 44 per cent O ₂ (m.l.)	68	68	65.6	93.6	91.1	5.65	1.6.3	60.2	7.132	7.308	11.1	120	
7	5 min 11.5 per cent O ₂ (m.l.)	170	115	41.7	91.7	7.27	59.0	49.0	7.360	7.309	7.309	11.7	150	
8	6 min 11.5 per cent O ₂ (m.l.)	90	117	50.3	96.0	7.93	111.8	48.5	7.362	7.290	7.290	1.4	120	
9	7 min 11.5 per cent O ₂ (m.l.)	75	103	51.6	91.9	6.60	59.1	41.0	7.460	4.01	11.6	11.6	100	
10	8 min 11.5 per cent O ₂ (m.l.)	50	119	61.0	91.0	6.60	59.1	41.0	7.460	4.01	11.6	11.6	100	
11	9 min 11.5 per cent O ₂ (m.l.)	40	119	61.0	91.0	6.60	59.1	41.0	7.460	4.01	11.6	11.6	100	
12	10 min 11.5 per cent O ₂ (m.l.)	40	119	61.0	91.0	6.60	59.1	41.0	7.460	4.01	11.6	11.6	100	
13	11 min 11.5 per cent O ₂ (m.l.)	40	119	61.0	91.0	6.60	59.1	41.0	7.460	4.01	11.6	11.6	100	
14	12 min 11.5 per cent O ₂ (m.l.)	40	119	61.0	91.0	6.60	59.1	41.0	7.460	4.01	11.6	11.6	100	
15	13 min 11.5 per cent O ₂ (m.l.)	40	119	61.0	91.0	6.60	59.1	41.0	7.460	4.01	11.6	11.6	100	
16	14 min 11.5 per cent O ₂ (m.l.)	40	119	61.0	91.0	6.60	59.1	41.0	7.460	4.01	11.6	11.6	100	
17	15 min 11.5 per cent O ₂ (m.l.)	40	119	61.0	91.0	6.60	59.1	41.0	7.460	4.01	11.6	11.6	100	
18	16 min 11.5 per cent O ₂ (m.l.)	40	119	61.0	91.0	6.60	59.1	41.0	7.460	4.01	11.6	11.6	100	
19	17 min 11.5 per cent O ₂ (m.l.)	40	119	61.0	91.0	6.60	59.1	41.0	7.460	4.01	11.6	11.6	100	
20	18 min 11.5 per cent O ₂ (m.l.)	40	119	61.0	91.0	6.60	59.1	41.0	7.460	4.01	11.6	11.6	100	
21	19 min 11.5 per cent O ₂ (m.l.)	40	119	61.0	91.0	6.60	59.1	41.0	7.460	4.01	11.6	11.6	100	
22	20 min 11.5 per cent O ₂ (m.l.)	40	119	61.0	91.0	6.60	59.1	41.0	7.460	4.01	11.6	11.6	100	
23	21 min 11.5 per cent O ₂ (m.l.)	40	119	61.0	91.0	6.60	59.1	41.0	7.460	4.01	11.6	11.6	100	
24	22 min 11.5 per cent O ₂ (m.l.)	40	119	61.0	91.0	6.60	59.1	41.0	7.460	4.01	11.6	11.6	100	
25	23 min 11.5 per cent O ₂ (m.l.)	40	119	61.0	91.0	6.60	59.1	41.0	7.460	4.01	11.6	11.6	100	
26	24 min 11.5 per cent O ₂ (m.l.)	40	119	61.0	91.0	6.60	59.1	41.0	7.460	4.01	11.6	11.6	100	
27	25 min 11.5 per cent O ₂ (m.l.)	40	119	61.0	91.0	6.60	59.1	41.0	7.460	4.01	11.6	11.6	100	

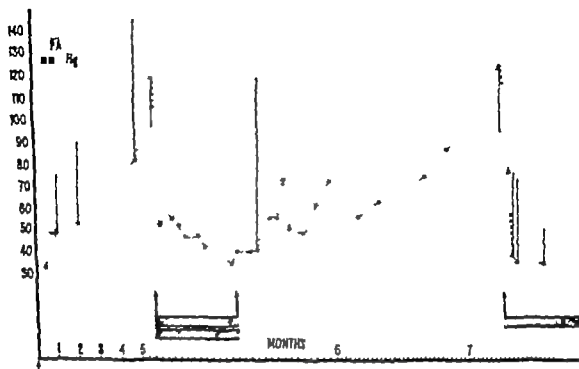


Fig. 1 Mean pulmonary arterial pressure is plotted against time. Each star represents an individual observation. The spright arrow indicates response to acute hypoxia and the downward arrows represent the response to the acute administration of mixtures high in oxygen.

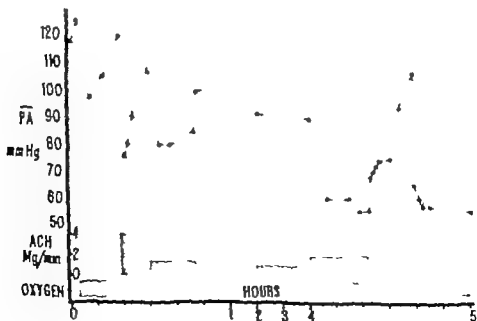


Fig. 2 Response of mean pulmonary arterial pressure to acetylcholine (ACh) and oxygen. Note progressively lower pressure with repeated pharmacologic treatment.

Table 11 Summary of pharmacologic treatment in Calf No 36

Date (1967)	Treatment	Mean PA pressure (mm Hg)	
		Before	During or After
October 3	Acetylcholine 1 mg/min 1:00 P.M. to 3:00 P.M.	120	60
	Oxygen 10 l/min 8:00 A.M. to 6:00 A.M. October 4	64	50
October 4	Acetylcholine 8.20 A.M. () tube out	52	40
	Oxygen 10 l/min 5:30 P.M. to 6:00 A.M. October 5	—	52
October 5	Acetylcholine 1.5 mg/min 9:25 A.M. to 4:30 P.M.	52	50
	1.5 mg/min 11:15 P.M. to ?	47	40
	Oxygen 3 l/min 5:45 P.M. to 7:00 A.M. October 6	58	47
October 6	Acetylcholine 1.1 mg/min 6:30 P.M. to 10:00 A.M. October 7	45	47
	Oxygen 7 l/min 6:00 P.M. to 8:00 A.M. October 7	55	43
October 7	Oxygen 7 l/min 9:30 P.M. to	52	45
October 8	Oxygen 7 l/min 5:00 P.M. to 7:00 A.M. October 9	47	41
October 9	No treatment	—	—
October 10	Acetylcholine 1.5 mg/min 8:30 P.M. to 3:00 A.M. October 11	—	—
	Oxygen 1 l/min 8:00 P.M. to 12:00 P.M. October 11	47	4
October 11	Acetylcholine 1.5 mg/min 7:15 to 9:00 A.M. October 12	42	—
	Oxygen 7 l/min 7:30 P.M. to 10:30 A.M. October 12	—	—
October 12	Acetylcholine 1.5 mg/min 1:00 P.M. to 7:00 A.M. October 13	—	—
	Oxygen 7 l/min 3:30 P.M. to 8:00 A.M. October 13	—	—
October 13	Acetylcholine 1.8 mg/min 12:00 P.M. to 10:00 P.M.	33	—
	Oxygen 7 l/min 3:30 P.M. to 8:00 A.M. October 14	—	37
October 14	Acetylcholine 1.5 mg/min 12:45 P.M. to 7:00 A.M. October 15	37	—
	Oxygen 7 l/min 3:00 P.M. to 9:00 A.M. October 15	—	—
October 15	Acetylcholine 1.5 mg/min 8:30 P.M. to 4:00 P.M. October 16	40	—

12 day period. Mean pulmonary arterial pressure was 52 mm Hg on the second day before treatment was continued. There was a further slow progressive decrease in mean pulmonary arterial pressure to 33 mm Hg after 11 days of therapy. On the 1st day of treatment mean pulmonary arterial pressure was 40 mm Hg. This was associated with an increase in mixed venous saturation to 64 per cent from a low value of 43.7 per cent prior to therapy, suggesting a narrowing of the arteriovenous oxygen difference and increased cardiac output.

After discontinuation of therapy there was a slow rise in mean pulmonary arterial pressure to 48 mm Hg at 2 weeks and to 122 mm Hg at 7 weeks. This was associated with a rise in mean venous pressure to 10 mm Hg and a reduction in cardiac output as manifested by widening of the arteriovenous oxygen difference to 7.65 volumes per cent. Pao_2 was 38.2 mm Hg and unchanged from prefailure values. Clinically the animal was in marked

distress with severe dyspnea on minimal exertion, mild acute distended neck veins and nose breathing.

Fig. 3 shows the time course in relation ship to altitude of the trip from Denver to Houston. One hour after arrival at Houston mean pulmonary arterial pressure was 75 mm Hg and Pao_2 had increased to a normal sea level value of 94 mm Hg. It may be noted from Fig. 3 that the animal had then been below 1,000 feet in altitude for approximately 11 hours. Sixteen hours after arrival at Houston mean pulmonary arterial pressure was 38 mm Hg and after 40 hours 35 mm Hg. Mean venous pressure decreased to 4 mm Hg. Sixteen hours after arrival the arteriovenous oxygen difference had narrowed to a normal value of 5.2 volumes per cent. Clinically the animal was markedly improved being able to stand considerable exertion without obvious dyspnea. One week later mean pulmonary arterial pressure was 34 mm Hg and at 4 months 40

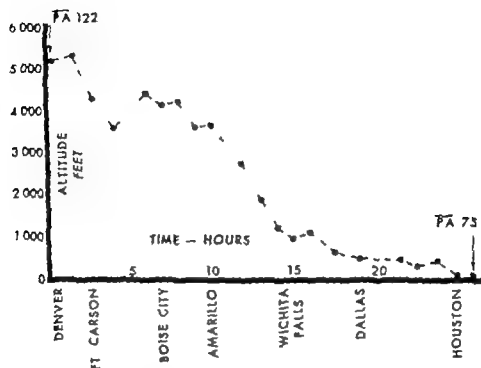


Fig. J. Chart illustrating the rate of change in altitude during trip from Denver to Houston.

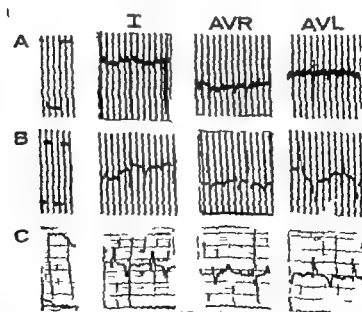


Fig. 4. Serial electrocardiograms in calf No. 36 taken to sea level. A: Dec. 9, 1964, mean PAP = 10 mm Hg. B: Dec. 11, 1964, mean PAP = 35 mm Hg. C: Dec. 1, 1965, mean PAP = 34 mm Hg. Note rightward shift of QRS axis occurring within 8 days after arrival at sea level. The first tracing (Dec. 9, 1964) taken 1 h or after arrival in Houston is identical with the tracing of tained immediately previous to leaving Denver (STD = 1 m).

mm Hg. Moreover serial electrocardiograms revealed a progressive leftward shift of the QRS axis (Fig. 4).

Discussion

In our previous study it was shown that ligation of the left pulmonary artery in the newborn calf resulted in progressive pulmonary hypertension when performed in Denver at an altitude of 5 000 feet.¹ Subsequent attempts to reproduce these results at sea level were unsuccessful.⁴ However when calves in which ligation of the left pulmonary artery had been performed at sea level were transported to Denver progressive pulmonary hypertension developed. This indicated that whereas the increased pulmonary blood flow consequent to ligation of the left pulmonary artery at sea level was an insufficient stimulus to produce pulmonary hypertension the addition of the lower P_{AO_2} of 5 000 feet provided the necessary stimulus for the production of progressive pulmonary hypertension. Thus at an altitude of 5 000 feet ligation of the left pulmonary artery in the newborn calf provides a useful model for the study of hypoxic pulmonary hypertension.

Furthermore it has been shown that infants under 2 years of age with ventricular septal defects and pulmonary hypertension who reside at an altitude of 5 000 feet have nearly twice the pulmonary vascular resistance of those residing at sea level. The difference in resistance was thought to be attributable to greater pulmonary blood flow at sea level because of the higher P_{AO_2} . Consequently there is additional evidence in human subjects with underlying disease affecting the pulmonary circulation that the mild hypoxia of 5 000 feet may further alter pulmonary vascular resistance.

By contrast in normal subjects mean pulmonary arterial pressure is only slightly increased between sea level and 5 000 feet being 12 and 16 mm Hg respectively but at an altitude of 10 150 feet the mean pressure is significantly higher being 25 mm Hg.⁴ Similarly in normal calves there is little difference between pulmonary arterial pressure at sea level and that at 5 000 feet but if the animals are taken to 10 000 feet pulmonary hypertension de-

velops with mean pulmonary arterial pressures of 45 mm Hg after 2 months and 60 mm Hg by 6 months.⁴ Moreover it has been shown that progression of the pulmonary hypertension can be accelerated by chronic exposure to an altitude of 12 700 feet.⁴

The reversibility of such hypoxic pulmonary hypertension in both normal man and calves has also been reported. Thus in a 16 year old girl who had a resting mean pulmonary arterial pressure of 44 mm Hg at 10 150 feet a mean pressure of 17 mm Hg was recorded 11 months after she had gone to sea level.⁷ In addition Peñaflora and associates⁸ reported in 11 subjects a reduction in mean pulmonary arterial pressure from an average value of 24 mm Hg at 14 200 feet to 12 mm Hg 2 years after their arrival at an altitude of 500 feet. In neither of the above mentioned studies was it possible to assess the rapidity of the reduction in pulmonary arterial pressure because of the long time intervals. Of interest in this regard is a report by Kunda and associates⁹ on serial studies in calves with hypoxic pulmonary hypertension and right heart failure (brisket disease) at an altitude of 4 500 feet. Studies were performed 2 days after arrival in Salt Lake City and then at 5 day intervals. Initial mean pulmonary arterial pressures ranged from 45 to 115 mm Hg. All animals experienced a reduction in pulmonary arterial pressure but the time sequence of catheterization did not allow a precise evaluation of the rate of fall in pressure since studies were not carried out prior to leaving high altitude or immediately upon arrival in Salt Lake City. Furthermore there are no data on the rate of change in pressure in animals suffering from brisket disease which have been taken to sea level.

That a rapid decrease in pulmonary arterial pressure is possible however is suggested by the recent report of Emmanouilides and associates¹⁰ who showed that in the human newborn infant at sea level the major decrease in pulmonary arterial pressure occurred within 24 hours after birth. Moreover Averill and associates¹¹ have noted a similar rate of change in newborn puppies studied at an altitude of 5 000 feet. The present study has shown

the rapidity with which hypoxic pulmonary hypertension may decrease upon exposure of the subject to the pO_2 present at sea level. Thus within 1 hour after arrival at Houston, mean pulmonary arterial pressure had decreased to 75 mm Hg from a value of 122 mm Hg in Denver, and after 16 hours, to 38 mm Hg.

Whether these rapid and extensive changes in pressure were due to anatomic changes in the pulmonary arteries and/or relief of vasoconstriction remains to be determined. In previous studies it was shown that when cattle with brucellic disease were given oxygen to breathe while still at high altitude, only a slight fall in pulmonary arterial pressure was achieved.⁴ This failure to reduce pressure further was attributed to the presence of anatomic changes within the pulmonary arteries, whereas the additional elevation of pressure which was alterable by oxygen was attributed to vasoconstriction. If the changes in pressure observed in the present study were due in large part to anatomic alterations, this would suggest that within hours marked alterations may occur in cytoplasmic mass. That anatomic changes

(medial hypertrophy) may be present in normal subjects residing above an altitude of 10 000 feet has been shown by Naeije¹ and Arias Stella and Sakdafa.¹² However, that vasoconstriction played a role was evidenced by the acute response to pharmacologic agents. Moreover, postmortem pulmonary arteriography has suggested a considerable degree of vasoconstriction in addition to medial changes (Fig. 3). The fact that pressure could be altered so dramatically after but hours of treatment suggests that some degree of reversible contracture was associated with the vasoconstriction and anatomic changes. Further studies are now in progress to evaluate the histologic changes appearing during these rapid changes in pressure. The rapid decrease in pulmonary arterial pressure noted in this study upon descent to lower altitude is in contrast to the slower rate of increase in pulmonary arterial pressure observed upon ascent to high altitude which takes weeks to months to develop.^{2,7,14}

The calf in the present study developed progressive pulmonary hypertension during a time course similar to that previously re-

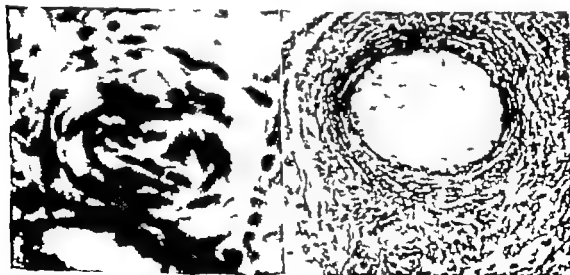


Fig. 5. Left: Muscular pulmonary artery from upper lobe of calf with light hypoxia of the left pulmonary artery which died with heart failure and progressive pulmonary hypertension. Right: Muscular pulmonary artery from right lower lobe of same animal. Vessel has been injected with Macropaque and gelatin. As to that with distention of the vessel the medial layer is much less prominent than in the unperfused contracted vessel shown at left. These studies suggest that, in addition to the increased size and number of medial cells, vasoconstriction plays an important role in the development of pulmonary hypertension.

ported.¹ In that study it was also shown that the acute administration of intravenous acetylcholine was effective in reducing pulmonary hypertension in calves as was the administration of mixtures high in oxygen.¹ Moreover it was shown that the combination of acetylcholine and oxygen was more effective than either alone. It has also been shown in normal individuals residing at an altitude of 10 000 feet that a combination of tolazoline and oxygen was more effective than either agent given separately.⁴ Tolazoline was employed in the present study without effect and previous papers have noted that it is ineffective in the calf.^{1,7}

Of interest was the demonstration that the results of acute administration of either acetylcholine and/or mixtures high in oxygen were not indicative of the responses that could be obtained with chronic administration. Thus when the animal achieved a resting mean pulmonary arterial pressure of 120 mm Hg at 5 months of age acute administration of oxygen resulted in a decrease to 96 mm Hg and of acetylcholine to 75 mm Hg. However after a 2 hour infusion of acetylcholine plus readministration of oxygen mean pulmonary arterial pressure was reduced to 55 mm Hg. After 11 days of intermittent chronic therapy with acetylcholine and nasal oxygen mean pulmonary arterial pressure reached a low of 33 mm Hg. Furthermore after treatment was discontinued 7 weeks were required before pulmonary arterial pressure returned to the control level of 120 mm Hg. Again acute administration of oxygen did not reflect the potential reduction possible in that mean pulmonary arterial pressure decreased from 122 to but 93 mm Hg in association with an increase in P_{102} from 58.2 to 90 mm Hg. However within 1 hour after arrival in Houston mean pulmonary arterial pressure had decreased to 75 mm Hg in association with a normal sea level P_{aO_2} of 94 mm Hg. As shown in Fig. 3 the animal had been below 1 000 feet for approximately 11 hours. Sixteen hours after arrival in Houston mean pulmonary arterial pressure had decreased to 38 mm Hg. Thus further decrease in pressure was not associated with any further change in P_{aO_2} . Cardiac function

was improved as manifested by a decrease in venous pressure and an increase in cardiac output. Clinically the animal's exercise tolerance was markedly improved.

Thus the results of this study as well as observations in normal man have shown that hypoxic pulmonary hypertension is in large part reversible and indicate the feasibility of chronic pharmacologic treatment of hypoxic pulmonary hypertension. It has been reported that chronic observation of pulmonary arterial pressure at the bedside is a feasible procedure and relatively easily performed.¹⁴ A number of clinical situations would appear to be susceptible to chronic treatment and observation as performed in this study. Studies in children with hypoxic pulmonary hypertension and cystic fibrosis have shown the feasibility of acute and chronic therapy with intravenous tolazoline for the reduction of pulmonary hypertension.¹⁵ In the same study the importance of observing the effects of sleep on pulmonary arterial pressure was also shown. Chu and associates¹⁷ have shown that the repeated administration of acetylcholine is effective in children with respiratory distress syndrome and more recently Cotton¹⁸ has shown the usefulness of tolazoline in this syndrome with benefit presumably resulting from relief of pulmonary arterial vasospasm. Naeve and Blum¹⁹ have reported a syndrome characterized by premature closure of the foramen ovale associated with normal development of the left ventricle in which severe pulmonary hypertension appeared to be responsible for death. Repeated administration of tolazoline to such infants might be life saving. Hypoxic pulmonary hypertension is a significant problem in patients with hypoventilation resulting from restrictive chest disease, obesity, or chronic bronchitis and it is suggested that chronic pharmacologic therapy may prove to be useful in such patients.^{16,20} Recently we studied a patient with pulmonary hypertension associated with obesity and hypoventilation in whom ethamivan appeared to be effective in improving ventilation and decreasing the pulmonary hypertension.¹ Furthermore in children with congenital heart disease and reactive pulmonary hypertension chronic therapy

both preoperatively and postoperatively may be beneficial

Summary

In this study the effect of chronic pharmacologic treatment of hypoxic pulmonary hypertension was evaluated. The responses to acute pharmacologic treatment were considerably less than the responses to chronic treatment. These results illustrate the feasibility of chronic pharmacologic treatment for the reduction of hypoxic pulmonary hypertension. Furthermore, these studies confirm the importance of vasoconstriction in chronic hypoxic pulmonary hypertension and the rapidity with which pulmonary arterial pressure may decrease when the hypoxic stimulus is blocked or removed.

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Physiologic evidence concerning the re-entry hypothesis for ectopic beats

Andrew G Wallace MD
Robert J Vignone BS
Durham N C

Premature beats particularly those of ventricular origin are a commonly encountered abnormality of cardiac rhythm. Although many of the pertinent factors which may account for these disturbances have been elucidated from microelectrode studies a demonstration of actual mechanisms in the intact heart is lacking.

The phenomenon of coupling indicates that this type of extrasystole probably does not arise *de novo* from an independently discharging pacemaker. Rather the coupled beat appears to be initiated in some way by activity of the preceding cycle.¹ The concept of re-entry has been proposed to account for coupled extrasystoles. According to this hypothesis recovery of excitability is presumed to occur in a nonuniform manner so that a succeeding impulse can mutually be refracted from areas which have not fully recovered but later enter these areas during the relative refractory period when propagation is slow. If conduction is sufficiently slow adjacent myocardium could then recover and the slowly propagating impulse could emerge from the depressed zone to initiate the extrasystole.

The studies described in this report were designed to test the re-entry hypothesis by

creating a discrete and reversible area of nonuniform recovery within the intact ventricle. A focal reduction in temperature was selected because it seemed to be likely that this alteration would result in a substantial dispersion of refractory periods at the junction between warm and cold muscle. The consequences of this intervention were found to include marked local alterations in recovery and conduction, intramural block, and re-entry.

Methods

Studies were performed on 10 healthy dogs which weighed 11 to 15 kilograms. The animals were anesthetized with thiopental 10 to 20 mg per kilogram and ventilated with a Harvard respirator. A mid sternal thoracotomy was performed and the pericardium was used to cradle the heart. The sinus node was crushed to slow the intrinsic heart rate. Pacing wires were attached to the right atrial appendage and connected through an isolation unit to a set of Tektronik pulse generators programmed to drive the atrium at a constant rate. A premature atrial beat could be introduced at any desired interval after each sixth basic stimulus.

A 2 by 2 cm silver coil was sutured to

From the Department of Medicine and the Department of Surgery, Duke University Medical Center, Durham, N. C.
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the anterior surface of the left ventricle. Water at varying temperatures could be circulated through the coil at selected rates to produce a local zone of controlled myocardial hypothermia. Myocardial temperatures under the coil were measured (to the nearest 0.5 C) at 2 mm intervals between endocardium and epicardium with a needle thermistor advanced through the coil. The position of the thermistor was determined at the end of each experiment.

A multipolar electrode of the type designed by Scher² was advanced through the coil with its tip in the cavity of the left ventricle. Care was taken to position the cooling coil so that the electrode did not enter a papillary muscle. Wires from the electrode were connected to a switching device which permitted simultaneous bipolar recordings from any two sets of adjacent contacts. The electrode consisted of 10 contacts each separated by approximately 1 mm. The recording contacts were selected in a manner so that, when the contact nearest the endocardium was negative with respect to its pair a negative deflection was recorded.³ An additional electrode was implanted on the epicardial surface of the right ventricle and used as a reference for timing purposes (Fig. 1).

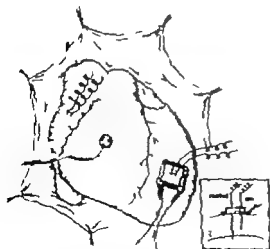


Fig. 1 Experimental preparation. Pure wires on right atrium. Reference electrode on right ventricle. Silver cooling coil on left ventricle. Inset shows cross section through cooling coil and left ventricle with the Scher electrode and thermistor in position.

Signals from each electrode were amplified with special Tektronix 122 A C coupled preamplifiers, displayed on a four channel oscilloscope and recorded on a multi-channel Consolidated oscillograph at a paper speed of 8 inches per second. The frequency response of the channels used for recording from the Scher electrode was flat from 0.5 to 1000 cps. Frequencies below 80 cps were filtered on the channel used to record from the right ventricular surface electrode in order to sharpen the signal. A Lead II ECG also was recorded.

The sequence of excitation under the coil was determined by scanning each pair of contacts between endocardium and epicardium and noting the interval between local depolarization and the reference point on the right ventricle. This sequence was determined for basic atrial beats (A₁) and for premature atrial beats (A₂). The multipolar electrode also was used to measure the sequence of recovery at each recording point under the coil following A₁. This was accomplished by first noting the time of local activation at each pair of adjacent contacts and then scanning the interval after local depolarization with a 5 msec pulse of twice threshold delivered through the same contacts. The effective refractory period at each point was measured as the interval between local depolarization and the time at which a propagated response could be induced by the pulse. Observations were made when the myocardium was warm during local cooling and after rewarming.

Results

Fig. 2 shows an example of the effects of the perfusion of ice water on temperatures under the coil. At zero flow there was no detectable difference in temperature between the endocardium (0 mm) and the epicardium (10 mm). When ice water was perfused through the coil at a flow of 30 ml per minute there was no change in temperature at the inner 2 mm of the wall but a progressive fall in temperature was observed as the probe was withdrawn to the epicardium resulting in a transmural temperature gradient of 1°C at a flow of 60 ml per minute. Endocardial temperature fell...

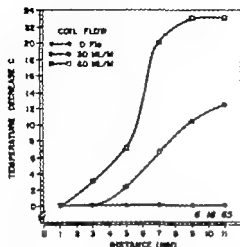


Fig. 2 Effect of perfusing ice water through the coil on transmural temperature gradient. Distance from the cavity is plotted on the horizontal axis. The temperature is plotted on the vertical axis and expressed as deviation from a 37° temperature.

was a more marked fall in temperatures in the mid and outer portions of the wall resulting in a transmural gradient of 23°C. The sigmoid curves relating change in temperature to distance reveal that large temperature gradients existed over distances as short as 2 mm.

An example of the effect of cooling on the sequence of excitation under the coil is shown in Fig. 3. The atrium was paced at a rate of 72 per minute. After each sixth basic beat a premature stimulus was delivered to the atrium which resulted in a propagated ventricular response 350 msec after the basic ventricular beat. In panel A of Fig. 3 the line described by the solid circles shows the sequence of ventricular activation for the basic beat (A_1) prior to cooling. The impulse required 22 msec to pass from endocardium to epicardium. The spread of activity during the premature supraventricular beat (A_2) is described by the line connecting the open circles. Although slight differences were noted during A_2 , no point varied by more than 3 msec when compared to A_1 .

In panel B of Fig. 3 the sequence of activity during cooling, at 30 ml per minute is shown. Heart rate and the A_1 A_2 interval were the same as in panel A. Cooling did not delay A_1 at the endocardium or over a distance of 4 mm into the

wall. In the outer half of the wall excitation was delayed by several milliseconds so that the impulse required 31.5 msec to reach the epicardium. A_2 reached the endocardium without delay during cooling, however propagation was markedly slowed in the outer half of the wall so that the interval between endocardium and epicardium was 63 msec.

When ice water was perfused through the coil at flow rates of 30 ml per minute or greater there always was some delay of epicardial excitation during A_1 . However at flow rates of 15 ml per minute the sequence of depolarization during A_1 was normal. The occurrence of marked intramural delay during A_2 as well as the phenomenon which will be described subsequently could be produced readily at flow rates of 15 ml per minute and were not dependent on delayed epicardial excitation during A_1 .

The effect of cooling on propagation under the coil is demonstrated further by the electrograms shown in Fig. 4. Bipolar records were obtained from the endocar-

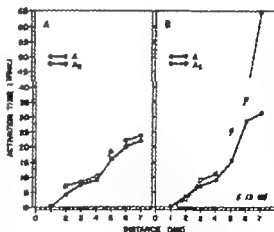


Fig. 3 Effects of perfusing ice water through the coil at 30 ml per minute on transmural activation times. Distance from the cavity is plotted on the horizontal axis and activation time is plotted on the vertical axis. The electrogram recorded from the first pair of contact in the endocardial surface (1 mm) was used as a time reference and arbitrarily designated 0 time. Panel A shows observations prior to cooling and panel B shows observations during cooling. Heart rate was 72 beats per minute. The interval between A_1 and A_2 was 350 msec. See text for further details.

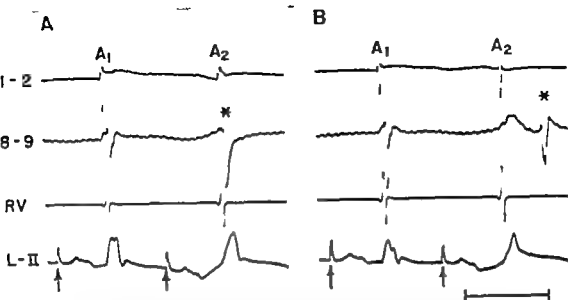


Fig. 4 Effects of perfusing ice water through the coil on intramural conduction. Panel A shows record prior to cooling and panel B shows record during cooling (15 ml per minute). 1-2 Refer to the electrogram recorded from the first two contacts in the endocardium. 8-9 Refer to the electrograms recorded from contacts in the subepicardial zone. RV Refer to the surface electrogram from the right ventricle. L-II Refer to electrocardiographic Lead II. In panels A and B A₁ is the last of a series of atrial premature beats, and A₂ is a premature atrial response 80 msec after A₁. Arrows denote pacing stimuli applied to right atrium. Time base = 200 msec.

dium (1-2) from near the epicardium (8-9) and from the epicardial surface of the right ventricle (RV). Lead II of the ECG also is shown. Panel A shows tracings of a basic beat (A₁) followed by a premature atrial beat (A₂) prior to perfusion of ice water through the coil. The interval between depolarization at the endocardium and that at the epicardium was 14 msec during both A₁ and A₂. Panel B shows tracings of a basic beat (A₁) and a premature atrial beat (A₂) after 10 minutes of perfusion of ice water. The A₁-A₂ interval was the same as in panel A. During A₁ the interval between endocardium and epicardium was 14 msec. During A₂ depolarization at the endocardium occurred normally, but the interval between endocardium and epicardium was prolonged to 100 msec.

Intramural delay of A₂ occurred only during cooling and could be shown to be a function of the A₁-A₂ interval. Thus when the A₁-A₂ interval was wide the sequence of excitation for both was identical. When the A₁-A₂ interval was shortened A₂ was delayed in the outer portions of the

wall as shown in Fig. 4. With further shortening of the A₁-A₂ interval no activity was recorded from the epicardium, indicating that propagation of A₂ had failed in the intramural portion of the wall. On several occasions an A₁-A₂ interval could be selected at which the block between the endocardium and the epicardium was intermittent or 2:1 in type.

Fig. 5 shows data from an experiment in which the effective refractory period after A₁ was determined at each point under the coil. The sequence of recovery before cooling is depicted by the closed circles and that observed during cooling is depicted by the open circles. Prior to cooling refractory periods at the different points varied from 215 to 44 msec. No consistent differences were noted between the endocardium and the epicardium. During cooling the refractory period of the epicardium was prolonged to more than 400 msec. Thus cooling, not only produced a marked lengthening of the effective refractory period in the outer portion of the wall but also resulted in a

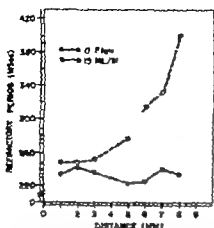


Fig. 5 Effect of perfusion of ice water through the coil of the effective refractory period at seven points between endocardium and epicardium. Distance from the origin is plotted on the horizontal axis. Effective refractory period after A are plotted on the vertical axis.

substantial increase in the local temporal dispersion of recovery.

In each animal during cooling an A_1 -A interval could be selected at which A was followed by nonstimulated ventricular extrasystoles. In any given animal the appropriate A_1 -A interval was one sufficiently short so that A was blocked on transit to the epicardium. When this condition obtained recording contacts were selected so as to display simultaneously activity from the endocardium and from a point in the wall just proximal to the level of block. In each instance in which a nonstimulated extrasystole was observed activity in the mid portion of the wall during A was delayed by more than 90 msec and was followed by re-excitation of the endocardium coincident with the onset of the nonstimulated ventricular extrasystole. Furthermore the polarity of the endocardial complex during re-excitation was reversed indicating that the local direction of spread was from epicardium to endocardium.

Illustrations of the above mentioned phenomena are presented in Figs. 6 and 7. Although no attempt was made to catalogue the frequency with which nonstimulated responses could be elicited they could be produced at will in every animal. If the A_1 -A interval was increased by an amount sufficient to permit A to reach

the epicardium nonstimulated responses were never observed. When the epicardial zone was rewarmed propagation of A returned to control values and nonstimulated ventricular extrasystoles could not be elicited at any A_1 -A interval.

In 7 of 10 dogs repetitive nonstimulated ventricular extrasystoles followed A_1 during cooling. These runs constituted short bursts of ventricular tachycardia and in each instance the first nonstimulated beat of the run originated from the region of the coil and the endocardial complex indicated inward spread. In 6 of these 7 dogs the run of tachycardia degenerated into ventricular fibrillation. Fibrillation could be converted to normal sinus rhythm in all instances by a single shock applied directly to the heart. Fibrillation was never observed during cooling in the absence of A and was never observed when the coil was warm regardless of the A_1 -A interval.

Discussion

The concept of re-entry finds its greatest support from observations concerning the mechanism of reciprocal rhythm or echoes. Ventricular echoes are bursts of supraventricular origin which can be initiated by a properly timed premature ventricular stimulus. The premature response is presumed to arrive at the A-V node when only some cells have recovered from the preceding beat. The impulse enters a group of fibers which has recovered and propagates slowly to the atrium. When the impulse reaches the atrioventricular junction it enters those elements of the node which were not used for retrograde conduction and returns over these fibers to re-excite the ventricle. A re-entry circuit within the node is possible because of the unequal refractory period of adjacent cells and consequent nonuniform recovery of excitability.^{4,5}

Schmitt and Erlanger⁶ were one of the earliest groups to suggest that re-entry might account for ventricular extrasystoles. They demonstrated that when the central portion of a long strip of muscle was depressed by potassium an impulse initiated at one end of the strip could be reflected from the depressed zone and return to re-excite the end from which it was initiated. The conditions required to demonstrate this behavior were slow con-

duction with unidirectional block in a part of the muscle. Although the work of Schmitt and Erlanger is quoted often with reference to re entry its applicability has been questioned because it seemed to be unlikely that conduction could be slow enough in

the intact ventricle to permit re entry with the usually observed coupling in intervals¹

The concept of a reentrant circuit created by nonuniform recovery of excitability has gained credence as a result of

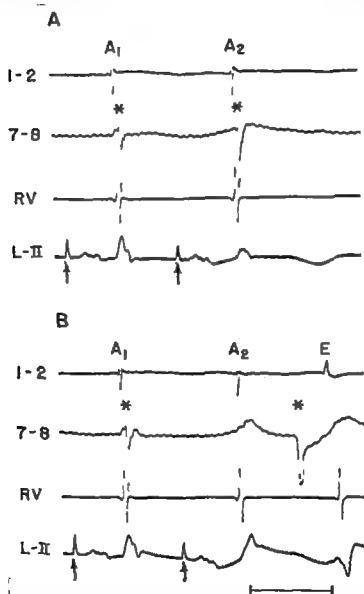


Fig. 6. Re-entry extrasystoles during cooling. Panel A shows record of activity during A₁ and A₂ prior to cooling. Panel B shows record of activity during A₁ and A₂ while cooling. 1-2 Refers to the electrocardiogram recorded between the first and second contacts in the endocardium. 7-8 Refers to the electrogram recorded from the seventh and eighth contacts. RV Refers to the epicardial lead on right ventricle. L-II Refers to Lead II ECG. Note that in panel B during cooling activity at 7-8 is delayed during A₂ by 150 msec and is followed by re-excitation of the endocardium (RV) which sustains a nonstimulated extrasystole. Time base = 200 msec.

recent experiments by Moe, Mendez and Han.¹⁰ These investigators demonstrated that the refractory period of the right bundle branch often exceeded that of the left bundle branch. When an appropriately timed premature stimulus was applied to the bundle of His the impulse was blocked in the proximal right bundle branch but propagated to the ventricles

over the left bundle branch. After cessation of the ventricles the right bundle branch was activated retrogradely and the retrograde impulse returned to re-enter the bundle of His. Although the exact course of the re-entrant pathway could not be established the circuit required participation of both bundle branches and was established only when the two branches

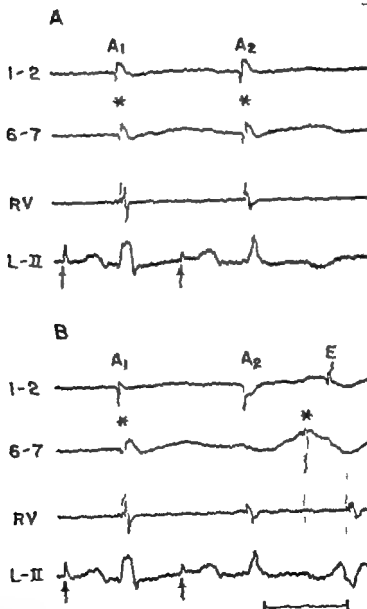


Fig. 7. Re-entrant extrasystole during cooling. Panel A shows A₁ and A₂ prior to cooling. Panel B shows A₁ and A₂ during cooling with an extra ectopic ventricular premature as in Fig. 6. Time base = 200 ms-sec.

were dissociated by a premature impulse which took advantage of their unequal refractory periods.

The results of recent experiments performed on isolated cardiac tissues also support the view that disturbances in conduction may be an important cause of ectopic rhythms. Hoffman¹ and his associates have presented convincing evidence that conduction can be sufficiently slow within a small network of fibers to permit re-entry. The mechanism of such slow propagation appears to be decremental conduction which has been defined as a phenomenon that results when an action potential becomes progressively less effective as a depolarizing stimulus to tissues in the pathway ahead. Decrement has been observed in nearly all cardiac tissues and the most frequent cause is that the action potential arises from a reduced transmembrane potential. Such a reduction may occur when the entire resting potential is less than normal or it may occur if membrane potential has not fully recovered from the preceding beat or if a fully polarized membrane develops spontaneous diastolic depolarization. The relevance of decremental conduction to the concept of re-entry has been emphasized recently by Hoffman.¹²

The experiments described in this report were designed to create a local area of nonuniform recovery and to test the response of this area to premature excitation. The results suggest that this intervention produced the necessary conditions for a re-entry circuit within the intact ventricle.

When a focal area of the left ventricle was cooled an appropriately timed premature supraventricular beat arrived at the endocardium under the coil at a normal time but was markedly delayed on transit to the outer portions of the wall. Intramural excitation was frequently delayed by as much as 90 to 100 msec. When these conditions obtained nonstimulated ventricular extrasystoles originated from the region of the coil. That the nonstimulated beats were indeed coupled to A was indicated by their absence when A₂ was not present.

The basic cycle length was sufficiently long so that A₁ always propagated from

endocardium to epicardium. Although excitation during A₁ was frequently delayed in the outer wall by cooling this was not a necessary condition for the occurrence of nonstimulated beats. The finding that activity persisted during A₁ with little or no delay indicates that muscle at all depths under the coil could be excited normally during cooling. The observations that cooling caused a prolongation of the effective refractory periods under the coil and that intramural delay or block of A₂ was a function of the A₁-A₂ interval indicate that the major factor responsible for delay or block was that A₂ encountered refractory tissue left in the wake of A₁. It seems to be reasonable to postulate that the delay of A₂ resulted from decremental conduction in tissues with a reduced membrane potential due to incomplete recovery. Intramural block may have resulted from progressive decrement or the abrupt change in refractory period at the junction between warm and cold muscle may have extinguished the propagating impulse.

Bipolar tracings from the transmural electrode were obtained in such a way that negative complexes indicated outward spread of the impulse whereas positive complexes indicated inward spread. During A activity at the endocardium was not delayed and the negative polarity of the complex indicated outward spread. After A there was re-excitation of the endocardium and the positive polarity of the complex indicated that the local spread was directed from epicardium to endocardium.¹³ This fact together with the observation that re-excitation of the endocardium occurred coincident with the onset of the nonstimulated beat suggest that the extrasystole originated from the intramural portion of the wall under the cooling coil. Although we cannot exclude the possibility that the experimental interventions led to pacemaker centers under the coil this seems to be highly unlikely in view of the known effects of hypothermia on pacemakers. Furthermore ectopic activity was never observed except when coupled to a critically timed A. These data suggest therefore that the ectopic beats were passively induced by A and resulted from re-entry of the delayed

impulse at the junction between warm and cold muscle.

In panel B of Figs. 4, 6, and 7 the intramural leads recorded what appears to be slow electrical activity immediately after the A complex at the endocardium. These slow waves were followed after considerable delay by a sharp deflection which indicates local excitation. The mechanisms underlying these slow changes remain to be explained. We have considered the possibility that they might represent a movement artifact but this seems to be unlikely since the electrode was held tightly in the coil and the coil was anchored securely to the heart. It also seems to be unlikely that the slow waves represented abnormal local action potentials since if tissue in close proximity to the contacts had depolarized coincident with A, it could not have recovered soon enough to permit a second depolarization at the times indicated by the rapid spikes. We believe that the most likely explanation for the slow wave is that a boundary existed between the fully depolarized myocardium and the locally blocked epicardial cold zone.¹¹ Flow of current across this boundary would be a function of the gradient in potential between the two regions. Slow waves of the type described were noted only at zones of marked delay and were not observed near the endocardium or in completely blocked epicardial regions. If the foregoing interpretation is correct then the local nature of the slow waves and the ability to record them with a bipolar lead of 1 mm separation imply that the boundary was relatively discrete and that the density of current created by the boundary was relatively intense.

Scherf and his associates¹² have shown previously that local cooling of the heart can cause multiple extrasystoles, bigeminal rhythm, and ventricular fibrillation. They suggested the possibility that these arrhythmias resulted from the formation of ectopic impulses perhaps as a consequence of a large negative after potential. The experiments described in this report confirm the observations of Scherf and associates but suggest an alternate mechanism based on re entry.

The observations of Scherf as well as those reported in this paper would appear

to have a bearing on the nature of arrhythmias during clinical hypothermia. Perfusion hypothermia is usually associated with intramyocardial temperature gradients¹³ and the incidence of ventricular arrhythmias can be reduced by techniques which reduce the magnitude of these gradients.¹⁴ Nonuniform cooling of the heart would be expected to have nonuniform effects on recovery of excitability. If phenomena of the type described in this report occur at junctional zones between areas of differing temperature then the possibilities by which such a nonhomogeneous system might respond in a disorganized manner are numerous.

In addition to temperature gradients a large number of other arrhythmic influences including coronary ischemia, sympathetic nerve stimulation, and overdoses of quinidine enhance the degree of nonuniformity of the ventricle. These influences also increase the likelihood of multiple responses or fibrillation after primary excitation.¹⁵⁻¹⁷ Although it has been assumed that fractionation of an impulse and re entry might occur, direct evidence that nonuniform recovery actually produces the conditions necessary for re entry in the intact ventricle has not been described previously. The experimental observations reported above provide support for the view that nonuniform recovery of excitability can be a factor of major importance in enhancing the propensity of a heart to the formation of extrasystoles and to fibrillation.

Finally, we believe that it is of interest that many features of the local sequence under the cooling coil resemble functional characteristics normally ascribed to the A-V node. Delay between endocardium and epicardium might be considered to be analogous to first degree A-V block, intermittent patterns to be similar to second degree block, and complete failure of A₁ to reach the epicardium to be analogous to third degree block. The conditions under which A₁ produced nonstimulated extrasystoles are similar to those characterizing echo responses which originate from the A-V node. The possibility that the junction between areas of differing excitability might demonstrate behavior similar to that of the A-V node including

re entry provides a conceptual model which could account for many clinically encountered disturbances in cardiac rhythm.

Summary

These experiments were designed to test the re entry hypothesis as a mechanism for the formation of extrasystoles. Studies were performed on 10 dogs with the heart exposed. Pacing wires were attached to the right atrium and connected to a set of pulse generators. The heart was paced at a basic frequency and a premature atrial stimulus was delivered after each sixth basic beat. A small silver coil was used to vary the temperature of a focal area of left ventricle and a multipolar electrode was advanced through the coil and used to record local depolarization.

When ice water was perfused through the coil temperatures in the outer portion of the ventricular wall were reduced. Cooling lengthened the effective refractory period under the coil and produced a marked increase in the temporal dispersion of recovery between endocardium and epicardium. When sufficiently premature stimuli were applied to the atrium the ventricular response reached the endocardium normally but encountered refractory muscle under the coil on transit to the epicardium. At the junction between warm and cold muscle propagation of the early response was markedly delayed and finally blocked near the epicardium. When the local delay was sufficiently great nonstimulated ventricular extrasystoles appeared which were coupled to the preceding beat. The nonstimulated extrasystoles originated from the region of the coil and were initiated by activity which was directed from epicardium to endocardium. On several occasions a nonstimulated beat was followed by multiple ventricular extrasystoles and by ventricular fibrillation.

These observations indicate that cooling of a discrete area of the left ventricle created the necessary conditions for re entry and that extrasystoles resulting from re entry were produced. These data also emphasize the potentially arrhythmic consequences of any influence which enhances nonuniform recovery in the heart

and suggest that the junction between areas of different refractory periods within the ventricle can demonstrate behavior similar to that of the normal A-V node.

The technical help of Mr James Manley, Mr Eleanor Zimmerman and Mr William Joyner was of great assistance in these studies.

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The selective uptake of Hg^{2+} -chlormerodrin in experimentally produced myocardial infarcts

Ralph J Gorton M D *

Laurence B Hardy B A **

Burley H. McCraw M.A.***

John R. Stokes FULTON

George D Lumb MD MRCP ****

Durham N C

The detection of myocardial infarcts in animals and human subjects by a photo-scanning technique has been reported recently by Carr and associates¹ and by Evans and associates.² With further developments the procedure holds promise of providing information in regard not only to the location but also to the extent and severity of myocardial damage. The following studies of experimental coronary arterial occlusion were designed to investigate the selective localization of certain radioactive chemicals in areas of myocardial damage and to correlate information gained by photo-scanning with gross radiologic and histologic examination of the tissues.

Methods

Gradual occlusion of the left circumflex artery was produced in a series of animals.

by surgical application of a sterile hygroscopic casein base plastic (Ammersoid) constrictor (1.57 mm in diameter) 5 mm from the ostium of this artery. As previously described, these constrictors close completely in 48 hours when placed in saline at 37 C.¹ Therefore occlusion of the arteries was considered to be complete in all animals by 60 hours.

Because the distribution of coronary arteries in swine is similar in many respects to that in man, mongrel pigs were selected for these experiments. A total of 76 animals with a weight range of 11 to 27 kilograms was used. Two animals were excluded because of pulmonary disease discovered at the time of operation and 1 was excluded for failure to recover from the anesthetic. Forty animals (50 per cent) died and represent the mortality figures for gradual occlusion of the left circumflex

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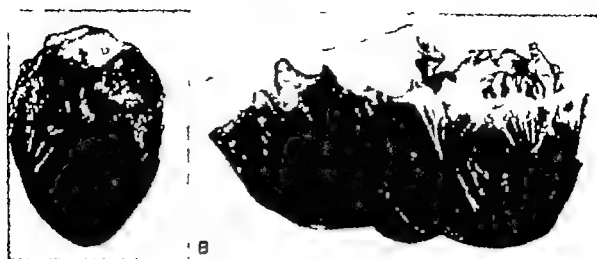


Fig. 1 Heart placed in the two positions used for photocanning: A Closed with anterior surface up (operative site in upper center); B Cut and unrolled with endocardium facing detector.

artery by this technique. Thirty-seven died in the first 3 days and the other 3 by the end of the fifth day.

The 33 pigs which survived the effects of arterial occlusion were divided into 3 groups in order to study myocardial infarcts at different time intervals after occlusion. Animals in Group I were sacrificed 3 to 5 days after surgical application of the constrictors; the intervals were 6 to 8 days for Group II and 9 to 17 days for Group III.

Twelve to 14 hours prior to scheduled sacrifice 1.6 millicuries of Hg^{203} chlormerodrin (Neohydria[®]) were administered into the external jugular vein of each pig. At autopsy each heart was examined for gross evidence of myocardial damage and the presence of other lesions was excluded. The excised hearts were washed free of blood. Photocanning was performed with the anterior surface of the intact heart toward the detector (Fig. 1A). The hearts were then cut and unrolled³ and the photocann was repeated with the endocardial surface toward the detector (Fig. 1B). A radioisotope photocanning system⁴ with a 5 inch diameter scintillation detector and a focusing collimator of 61 holes with a focal length of $3\frac{1}{4}$ inches was

used at 19 inches per minute. The pulse height analyzer window was 40 kev wide. No background cutoff was used. Brightness contrast and scale factor controls were set according to the maximum counts per minute in each heart (600 to 9,000 counts per minute). The primary aim was to obtain the greatest degree of contrast between areas of higher and of lower rates. Areas of higher count rates indicating selective uptake of the radioactive tracer were read on the photocann and graded 3, 2, 1 or 0 according to the degree of contrast between the dark (or hot) area and the rest of the myocardium.

Anatomic and histologic examinations were performed on all hearts and areas of infarction were described.

Nine hearts selected at random were perfused through the right coronary artery with a barium sulfate suspension (Micropaque[®]) at physiologic pressures.⁴ Roentgenograms of the closed and unrolled hearts demonstrated the distribution of the right coronary artery together with any collateral passage into the left coronary system. Comparative studies of the infarcted areas were made using these radiographs, the photocann and outline drawings of the naked eye appearances of the gross specimens.

Microopaque powder, Dainippon Ink Co. Ltd., Waco, Japan.
England. Supplied in U.S.A. by Picker X-Ray Corp.
White Plains, N.Y.

³ R. Bynolds and Sons Radiopharmaceutical Department,
New Brunswick, N. J. and Abbott Laboratories Radiopharmaceutical Department, Oak Ridge, Tenn.
⁴ Kuba-Vickers Inc., Cleveland, Ohio and F. Chad Instruments Company, Downs Grove, Ill.



Fig. 2 *A and B* Example of photoscans showing greatest degree of contrast between area of infarction and rest of myocardium (Grade 3). Shape of closed heart in *A* can be detected by slightly greater than background count of radioactivity in pericardial myocardium. Differences in count rate were too small in unrolled heart (*B*). Therefore perimeter of pericardium was drawn in for better orientation.



Fig. 3 *A and B* Photoscans showing easily detectable area of increased radioactivity but less degree of contrast than heart depicted in Fig. 2 (Grade 2).

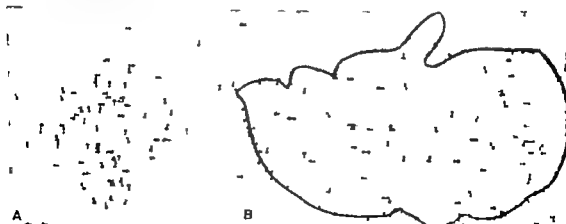


Fig. 4 *A and B* Photoscans showing easily detectable area of increased radioactivity but less degree of contrast than heart depicted in Fig. 3 (Grade 1).

Results

Of the 33 hearts examined by photo scanning, 26 (79 per cent) demonstrated areas of increased radioactivity. These were in the posterolateral wall of the left ventricle at the site expected for infarction from occlusion of the left circumflex artery. Series of hearts from 3 sham-operated animals and from 3 animals on which no operations were performed showed no localization of the tracer.

There was considerable variation in the degree of selective uptake of the radioactive material in the positive heart series. These differences were graded by four independent observers by visual inspection according to the degree of contrast between a hot area and the rest of the heart. The grading of all series was repeated on four occasions in order to avoid changes in standards of classification during the course of the study.

A series demonstrating the greatest degree of contrast (grade 3) is shown in Fig. 2. In Fig. 3 the hot area in the left ventricular myocardium is also easily detected but the contrast is less in degree (grade 2). Series without any area of selective uptake were given grade 0 (Fig. 4). Grade 1 was assigned to series with barely detectable or equivocal areas of increased uptake.

An inverse relationship between the age

of infarct and the degree of selective uptake of ^{45}Ca by the area of ischemic muscle is suggested by scan data summarized in Table 1. All series classified (grade 3) (those demonstrating the most obvious dark areas) were in Group I the animals sacrificed 3 to 5 days after application of the plastic constrictors. All but one of the series lacking any selective localization (grade 0) were from the hearts of animals in Groups II and III.

Areas of infarction identified by gross and microscopic examination showed excellent correlation with the results of photo scanning. The infarct site and overall size where it could be measured corresponded closely with the areas of selective localization of the radioactive tracer. Some evidence of infarction was seen in all hearts of Group II. In one heart of Group I no gross abnormalities could be detected probably because the changes were in a very early stage. In Group III gross changes were obvious in all but 3 hearts. In these healing had progressed sufficiently to make the identification of infarcts no longer possible.

Histologic evidence of myocardial damage was demonstrated in all hearts. This varied from cellular fragmentation and irregular staining reactions in Group I to evidence of healing, with fibroblastic activity in areas of myocardial necrosis in Group III. The hearts in Group II showed typical infarction with myocardial fiber necrosis and inflammatory infiltration.

Quantal evidence of myocardial damage could be demonstrated by routine histologic methods in one heart of Group I. It is of interest that this was the only heart in this group which gave a negative photomicrograph. The other series in animals of Group I the group in which total arterial occlusion had been present only 1 to 3 days and in which histologic changes were early but definite showed a high degree of contrast. In Group III where fibroblastic activity indicated healing and active myocardial fiber degeneration was minimal the photomicrographs showed a low degree or absence of localized radioactivity.

The radiographs of 9 hearts which were perfused with Microopaque showed areas of radiolucency surrounded by fluffy radiopaque areas which appeared to be

Table 1. Distribution of scan grades according to age of infarct

Group	Days	Number	Scan grade			
			3	2	1	0
I	3-5	13	5	5	2	1
II	6-8	10	0	2	6	2
III	9-12	10	0	0	6	4
		33				

Grade 3 denotes the best of areas of selective uptake of ^{45}Ca in the left ventricle. Grade 2 denotes areas of selective uptake of ^{45}Ca in the left ventricle. Grade 1 denotes areas of selective uptake of ^{45}Ca in the left ventricle. Grade 0 denotes no selective uptake of ^{45}Ca in the left ventricle.

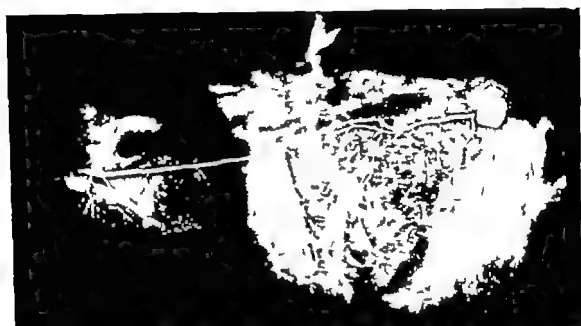


Fig. 5 Radiograph of unrolled heart showing area of translucency in posterolateral wall of left ventricle surrounded by fluffy zone. Perfusion with Micropaque was through the right coronary artery only. Constrictor can be seen on the left circumflex artery.



Fig. 6 Photomicrograph of heart seen in Fig. 5 shows area of increased radioactivity in same location as radiograph in loc. 5.

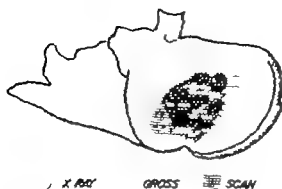


Fig 7 Outline drawing of same unrolled heart as in Figs 5 and 6 depicting position of infarct as seen by (a) naked eye (b) photocan hot area and (c) translucent and fluffy zone in radiograph

small vessels (Fig 5). These zones were in the posterolateral wall of the left ventricle and corresponded to the infarcts visible on gross examination and the hot areas detected by the photocans (Figs 5, 6 and 7). Because the left circumflex artery was occluded in all cases and the radioactive material was introduced only through the right coronary artery, the filling of the anterior descending and all other branches of the left coronary artery resulted from retrograde flow presumably through collateral vessels.

Certain factors other than age of the infarct and extent of myocardial damage may have influenced the results of the scanning. To determine whether radioactivity was contained mainly in vessels congested with stagnant blood, the coronary vessels of 4 scanned hearts were thoroughly flushed with physiologic saline solution and the scans were repeated.

Differences which were only barely noticeable could be detected in the pairs of respective scans. The areas of greatest radioactivity were not appreciably altered (Fig 8).

In 4 hearts microscopic evidence of slight but definite pericarditis was observed. However, 3 of the 4 hearts had been given scan grades of 0 to 1. This suggested that the role of inflammatory reaction involving the pericardium as a result of the operative procedure or concomitant with the myocardial infarct had little influence on the photocan. Two hearts which revealed hemorrhagic spots on gross examination had scan grades which varied from 0 to 3. None demonstrated hot areas localized to the sites of hemorrhage.

It was concluded therefore that the areas of selective localization of radioactivity were caused by myocardial damage produced as a result of the experimental gradual narrowing to occlusion of the left circumflex artery and not as a result of overlying pericarditis or vascular congestion or hemorrhage.

Discussion

Radioisotope photocanning depicts the spatial distribution of a radioactive chemical substance in an organ. Potentially, this procedure can aid in the evaluation of myocardial infarcts in patients and of experimentally produced infarcts in animals by providing objective information in addition to the electrocardiograms, enzyme levels and morphologic changes. Substances such as cesium 131 or iodinated (¹²⁵I) oleic acid materials taken up by normal myocardium can be used to depict infarcts as cold areas on heart scans.^{1,2}

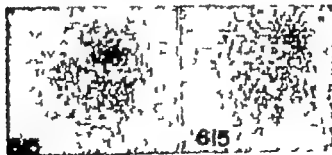


Fig 8 Photocans before (left) and after (right) coronary vessels were flushed with saline

To define areas of muscle damage in the excised hearts of laboratory animals with experimentally produced arterial occlusion, it is advantageous to use Hg^{203} chlormerodrin (Neohydrin) which is localised selectively in damaged myocardium. Such areas show up as dark or hot regions in comparison to the healthy myocardium. This material has been used to detect myocardial infarcts in living animals.⁷ Carr and associates⁸ who limited the tracer dose to 700 microcuries reported poor success in a series of patients with clinically diagnosed infarcts. Probably in all periods greater than 3 days had elapsed before the scans were performed.

Studies in living subjects are hindered considerably by the movements of the heart, the presence of radioactive indicator in the blood within the heart and in the lungs and the scattering by the tissues of the thoracic wall. It must be realized that in this study a larger tracer dose and scanning of excised washed animal hearts provided more optimum conditions for precise definition of the areas of necrosis.

The results of this study indicate that the radioactive tracer is able to reach portions of myocardium in which the main supply of blood is occluded and in which fiber degeneration is taking place. There is excellent correlation between hot areas on scans and zones of myocardial damage whether patchy or diffuse. Fibroblastic tissue in necrotic areas does not take up the radioactive material. Variation in the degree of uptake of the radioactive chemical in the hearts studied was caused mainly by differences in time after arterial occlusion and by differences in concentration and size of foci of necrosis in ischemic myocardium. The mechanism of selective localization in areas of myocardial fiber degeneration is still open to speculation. It is very unlikely that this is caused by vascular congestion, hemorrhage or overlying pericarditis. It may be that in areas of severely reduced blood supply capillary permeability is altered sufficiently to allow significant amounts of Hg labeled chlormerodrin to escape into the interstitial fluid so that it (or the mercury alone) can be bound by the sulfhydryl groups of the cell proteins.

Changes in staining properties of myo-

cardium are difficult to interpret by light microscopy in the period immediately after arterial occlusion and infarcts are not recognized with certainty within the first 2 days. Also it is difficult to estimate the size of infarcts by routine morphologic methods.⁹ On the other hand, distinct localization by radioisotope scanning was demonstrated frequently in hearts with infarcts showing only early cellular damage. Selective uptake of Hg^{203} was demonstrated in 12 of the 13 hearts in Group I. This indicates that this technique is of greatest usefulness in the identification of myocardial damage in the first 7 to 8 days after coronary occlusion.

Summary

Infarcts of the posterolateral wall of the left ventricle were produced in 73 swine by gradual occlusion of the left circumflex artery. Hg^{203} chlormerodrin was injected intravenously into 33 survivors 12 to 14 hours before sacrifice.

Photoscanning of intact and unrolled hearts showed a hot area of selective uptake of the isotope in the area of the infarct which correlated well in location and extent with pathologic observations. Intensity of selective uptake varied inversely with the length of time after application of the constrictor.

Photoscanning of selective uptake of Hg^{203} chlormerodrin is a valuable method for demonstrating areas of myocardial infarcts before replacement by fibroblastic tissue.

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Experimental revascularization of the entire heart

Evaluation of epicardiectomy omental graft and/or implantation of the internal mammary artery in preventing myocardial necrosis and death of the animal

Arthur V Lineberg MD*

Yutaka Kato MD

W J Pirozynski MD

Montreal Canada

The value of surgical techniques for the relief of coronary artery insufficiency has been greatly doubted. This has been partly because clinical evaluation of revascularization procedures is difficult due to the unpredictable character of the disease and partly because basic experimental methods of evaluation of an operative procedure have been lacking.

Many studies in our laboratory have made it quite clear that evaluation of a revascularization procedure by flow, back flow, ventricular fibrillation threshold, radioactive tracings and many other such methods left a great deal to be desired and for the most part could not be relied upon. For this reason over the years we have attempted to reproduce coronary artery occlusion by constructing the main stems at the locations at which obstructive disease occurs in human patients.¹⁻⁴

Experiments have been carried out until a 100 per cent lethal test has been developed as a result of slow occlusion of the main stems of all three coronary arteries by Ameroid constrictor.⁵

Besides survival of the animal from triple coronary artery occlusion the degree of myocardial necrosis in both ventricles has been used as objective evidence of the value of a revascularization procedure. In addition intra arterial injection studies using Schlesinger muscle⁶ have been carried out in order to outline the extracardiac coronary pathways which may or may not develop and which when present might explain any benefit that occurred as a result of a given revascularization procedure.

Experimental study

Various methods of revascularization were tested against the 100 per cent coronary artery Ameroid occlusion test.

A Control group In the control series of 70 animals there were 20 deaths; the spontaneous mortality was 100 per cent. The average survival time was 18.4 days; this was used as a base line to estimate the survival time. Survival time therefore becomes one of the criteria for the evaluation of various surgical procedures de-

* is with Department of Cardiology, Royal Victoria Hospital, Montreal, Canada.
and P. Lineberg, McGill University, Montreal, Canada.
Received for publication Oct. 22, 1964.
Address reprint requests to Dr. Lineberg, Department of Cardiology, Royal Victoria Hospital, Montreal, Quebec, Canada.

signed to relieve myocardial ischemia caused by triple coronary artery constriction

B Treated groups In all animals the Ameroid coronary artery constrictors were applied at the time of one of the following operative procedures

1 **EPICARDIECTOMY**—10 ANIMALS The epicardium was removed from the antero-lateral and posterior surfaces of both ventricles using specially designed epicardial scrapers which remove both layers of the epicardium without injury to the coronary vessels

2 **EPICARDIECTOMY AND SEROUS PERICARDIECTOMY**—10 ANIMALS The epicardium and serous layer of the pericardium were removed and the pericardium was closed

3 **EPICARDIECTOMY WITH INTERNAL MAMMARY ARTERY IMPLANTATION (VINEBERG)**—10 ANIMALS The left internal mammary artery was implanted into the anterior wall of the left ventricle The epicardium was removed from the remainder of the left ventricle The pericardium was left open

4 **FREE OMENTAL GRAFT OPERATION (VINEBERG)**—10 ANIMALS The entire heart was wrapped around by a graft of the greater omentum which was completely detached from its abdominal pedicle and the diaphragm was closed The omentum was not sutured to the heart but to the ascending aorta Epicardiectomy and serous pericardiectomy were not performed The pericardium was closed over the omental graft

5 **FREE OMENTAL GRAFT OPERATION PLUS EPICARDIECTOMY AND SEROUS PERICARDIECTOMY (VINEBERG)**—20 ANIMALS Extensive epicardiectomy of all surfaces of both ventricles was performed the serous layer of the pericardium was removed as was the reflection of the pericardium over the base of the aorta The greater omentum after its detachment from the transverse colon was wrapped around the heart It was fixed by multiple sutures to the ascending aorta and the heart The pericardium was closed

6 **FREE OMENTAL GRAFT PLUS EPICARDIECTOMY AND SEROUS PERICARDIECTOMY WITH INTERNAL MAMMARY ARTERY IMPLANTATION (VINEBERG)**—14 ANIMALS The

same technique as described under 2 3 and 5 was followed The left internal mammary artery was implanted into the anterior wall of the left ventricle The pericardium was resected anteriorly to prevent encroachment upon the internal mammary artery implant The omental graft was sutured to the free edges of the pericardium and to the anterior surface of the heart to avoid contact with the internal mammary artery

Postmortem studies

All animals underwent the following investigations

A Injection studies The chest was opened through the fourth intercostal space adhesions to the surface of the heart were not disturbed

The aorta was ligated above the diaphragm and at its junction with the left ventricle Care was taken not to damage anastomotic vessels between the aorta and the omental graft The thoracic aorta was cannulated proximal to the lower ligature New Schlesinger mass which does not pass through vessels that are less than 40 microns in diameter was injected at pressures that ranged between 100 and 120 mm of mercury filling the aorta and its branches above the diaphragm with dye Reflux of injection mass into the left ventricular cavity and coronary arteries was prevented by the ligature at the aortoventricular junction Thus radiopaque substances appearing in the coronary arteries could only have entered them by traversing extracardiac coronary anastomoses via the subpleural mediastinal and pericardial vessels X-ray films of the heart in situ before and after injection outlined the extracardiac coronary anastomoses when present

In the group of animals which had undergone the combined free omental graft and internal mammary artery implantation operation the internal mammary artery was ligated at the second intercostal space and cannulated distal to the ligature The radiopaque mass injected into the thoracic aorta filled mediastinal vessels and outlined omental coronary anastomoses as well as omental and/or mammary coronary anastomoses After injection and x-ray examination in situ the internal

mammary artery was injected under systolic pressure and the heart was x-rayed again in situ.

After removal of the heart the ascending aorta was resected with Schlesinger mass so as to fill vessels leaving the root of the aorta to anastomose with those in the omental graft. The ligature around the base of the aorta was not removed.

When the original aortic injection did not fill the entire coronary arterial tree then both coronary ostia were cannulated with metal cannulae and injected with Schlesinger mass. Separate x-ray films were taken after injection of each coronary artery.

After the injection mass had solidified the heart was unrolled in order to study homocoronary and intercoronary anastomoses as well as arterial channels which were formed to bypass the areas of Ameroid obstruction of the coronary arteries.

Multiple x-ray pictures taken between the injections of radiopaque Schlesinger mass have made it possible to outline numerous arteriolar and larger vessels and to study anastomoses formed between (a) the aorta and free omental graft (b) the graft coronary arteries and myocardium (c) mediastinal vessels pericardium graft and coronary myocardial vessels and (d) internal mammary artery myocardial arterioles and coronary arterioles.

Injection studies are not so definitive as survival of animals and ventricular muscle mass. However newly developed extracardiac channels through which oxygenated blood can bypass the proximal points of coronary artery occlusion may be outlined. In this study the injection mass was first introduced into the thoracic aorta in order to outline extracardiac coronary anastomoses. The filling of the coronary arterial tree through the aorta via mediastinal vessels may prevent satisfactory visualization of homocoronary and intercoronary anastomoses by later individual coronary artery injections. This occurs because the injection mass hardens before there is time to remove the heart and inject the coronary arteries. Thus the first injection should outline the important channels immediately. In this series our attention has been focused upon the extracardiac channels reaching the heart from

the mediastinal vessels. The demonstration of homocoronary and intercoronary arteries although desirable was regarded to be of secondary importance. In most instances these have also been outlined satisfactorily.

B Pathologic studies Each heart was examined grossly and microscopically for presence or absence and extent of ischemic myocardial damage. Multiple sections were taken from the right and left ventricles and the intraventricular septum.

The portions of each artery included in the Ameroid constrictors were investigated microscopically to determine the extent of narrowing of the lumina of the right anterior descending and circumflex coronary arteries. This has been recorded as the percentage occlusion of the original cross sectional area of the lumen. It has been expressed as an average occlusion for all three coronary arteries.

The patency of the implanted internal mammary artery was determined over its entire length including the myocardial tunnel.

Results

In this study we have attempted to establish simple criteria for estimating the value of a revascularization procedure. The four most important criteria of value are (1) survival time of animals (2) extent of damage to the myocardium after triple coronary artery Ameroid constriction (3) formation of extracardiac coronary anastomotic channels and (4) formation of a new surface cardiac distribution system (omental graft) connecting together right and left coronary systems and arteriolar zones.

1 Survival of animals The survival times of both the control series and the treated series are shown in Table I.

CONTROL GROUP In the control series the spontaneous mortality was 100 per cent.

TREATED GROUPS

1 In the series of 10 animals with epicardiectomy there was one death i.e. 90 per cent spontaneous mortality. The average survival was 16 days; there was one long term survivor sacrificed 266 days postoperatively.

2 In the second series of 10 animals in which the epicardium and serous layer of

Table I Survival time after triple coronary artery Ameroid constriction (control and treated)

	Number of animal series	Died				Sacrificed	
		Number of animal	Average number of days	Range in days	Spontaneous mortality (%)	23-440 days ()	Average number of postop days
Control	20	20	19	(9-22)	100		
Treated							
1 Epicardectomy	10	9	16	(7-28)	90	1-10	766
2 Epicardectomy and pericardectomy	10	8	30	(21-40)	80	2-20	215
3 Epicardectomy and internal mammary artery anastomosis	10	6	24	(15-39)	60	4-40	15
4 Free omental graft	10	6	20	(9-30)	60	4-40	235
5 Epicardectomy, pericardectomy and free omental graft	20	5	26	(17-37)	25	15-75	322
6 Epicardectomy, pericardectomy, free omental graft and internal mammary artery anastomosis	14	3	52	(19-50)	21	11-79	294
Total	94					31	

per cent free of coronary artery disease. Died postoperatively 71.5% 74.2 per cent control 83.3% 86.3 per

the pericardium were removed there were 8 deaths a spontaneous mortality of 80 per cent. Survival time averaged 30 days. Two long term survivors were sacrificed after 240 days postoperatively.

3 In the third group of 10 animals with epicardectomy and internal mammary artery implantation there were 6 deaths the spontaneous mortality was 60 per cent. The average length of survival was 24 days. There were 4 (40 per cent) long term survivors studied approximately 75 days postoperatively.

4 In the fourth series of 10 animals in which the free omental graft was wrapped around the heart there were 6 deaths a spontaneous mortality of 60 per cent. The average length of survival was 20 days. There were 4 long term survivors (40 per cent) studied on an average of 235 days postoperatively.

5 In the fifth series of 20 animals in which the epicardectomy, pericardectomy and free omental graft operations were performed there were 5 deaths a spontaneous mortality of 25 per cent. The average survival was 26 days. There were 15 long term survivors (75 per cent) three were sacrificed and studied on an average of 322 days postoperatively.

6 In the final series of 14 animals which underwent epicardectomy, pericardectomy, free omental graft application and internal mammary artery implantation there were 3 deaths a spontaneous mortality of 21 per cent. The average survival was 52 days. There were 11 long term survivors (79 per cent) three were sacrificed for study on an average of 294 days postoperatively.

² *Pathologic studies.* The pathologic findings of the control animals and those

Table II Tabulation of myocardial damage in experimental animals after triple Ameroid coronary artery constriction

	Number of animals in series	Animals dying spontaneously						Animals sacrificed			
		Number of animals	Myocardial damage				Number of surviving animals	Myocardial damage			
			None	Focal	Moderate	Massive		None	Focal	Moderate	Massive
Control	70	20	0	1	2	17					
Treated											
1 Epicardectomy	10	9	0	0	4	5	1	0	1	0	0
2 Epicardectomy and sero-pericardectomy	10	8	0	6	2	0	2	0	2	0	0
3 Epicardectomy and internal mammary artery implant	10	6	0	4	2	0	4	0	3	0	0
4 Free omental graft	10	6	0	0	1	5	4	0	3	1	0
5 Epicardectomy, sero-pericardectomy and free omental graft	20	5	0	2	2	1	15	5	10	0	0
6 Epicardectomy, sero-pericardectomy, free omental graft and internal mammary artery implant	14	3	0	2	0	1	11	7	4	0	0

which have been subjected to various surgical procedures are summarized in Tables II and III. A differentiation has been made between those animals which died from myocardial ischemia and those which were sacrificed many months after surgery.

For those animals which died spontaneously the average degree of coronary artery occlusion ranged from 71.3 to 76.2 per cent in all groups. In those animals which were sacrificed up to 469 days after surgery there appeared to be an increase in the degree of coronary artery occlusion as time went on and the average degree of cross sectional occlusion of the total coronary artery inflow tract ranged from 62.3 to 85.7 per cent for the survivors in all treated groups (Fig. 1).

The extent of myocardial damage was graded as follows: No myocardial changes 0 Focal infarcts (not grossly visible) +

Moderate or large infarcts—(grossly noticeable—confined to one surface) ++
Massive—transmural infarcts (gross and microscopic) +++

The animals were grouped according to the operative procedure and to the mode of death (i.e. spontaneous or sacrificed). In the control group 91 per cent of all animals showed mild to moderate myocardial damage in one or both ventricles at the time of spontaneous death.

Epicardectomy alone appears to have little beneficial effect on the prevention of massive myocardial infarction in either right or left ventricles in those animals which died spontaneously.

In the second group in which epicardectomy was combined with serous pericardectomy no massive infarction was present in the animals.

In the third group the implanted internal

Table III. Pathologic study

Triple coronary artery occlusion										Free coronary graft epicardial anastomosis percutaneous										Free renal anastomosis & artery anastomosis of gast										
Dog No	Survival days	R graft anast			L graft anast			Dog No	Survival days	R graft anast			L graft anast			Dog No	Survival days	R graft anast			L graft anast									
		Int	Ext	Post	Int	Ext	Post			Int	Ext	Post	Int	Ext	Post			Int	Ext	Post										
591	9							553	17							922	19							922	19					
49	11							910	73							446	79							446	79					
168	11							645	26							44	50													
778	13							973	26																					
324	14							113	37																					
124	17							R. 8	189																					
760	18							437	715																					
734	18							760	229																					
725	18							57	30																					
137	19							453	232																					
708	19							894	713																					
16	20							603	210																					
621	0							916	287																					
327	0							70	303																					
551	23							531	310																					
418	73							199	460																					
								46	46																					
136	75							482	468																					
115	26							90*	469																					
104	26							137	479																					

*Sept 4

+ = mild infarct; ++ = M. & S. or larger infarct; +++ = Massive or more extensive infarct

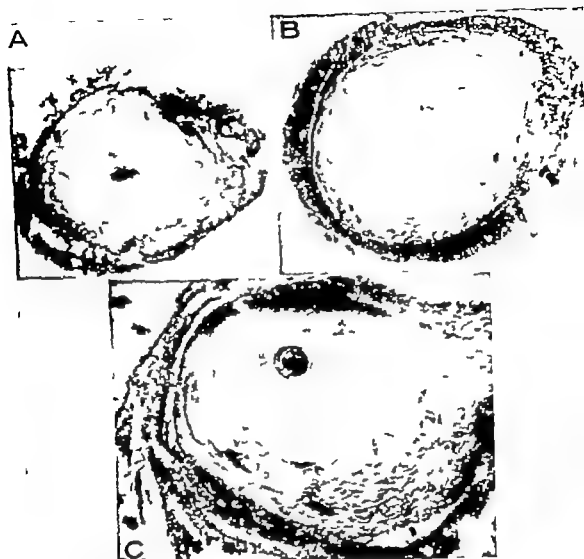


Fig. 1. Photomicrograph of sections taken from the sites of Ameroid placement on coronary arteries in Animal N 157 which was sacrificed 469 days postoperatively. *A* Photomicrograph section through the right coronary artery within the Ameroid; the degree of obstruction was 94.1 per cent. *B* Photomicrograph of section taken through the anterior descending branch within the Ameroid; the degree of obstruction was 78.5 per cent. *C* Photomicrograph of section taken through the circumflex coronary artery at the site of Ameroid constriction showing 90 per cent occlusion of the lumen. The average degree of cross-sectional occlusion of the total coronary artery inflow tract in those animals that were sacrificed ranged from 87.3 to 86 per cent.

mammmary artery combined with epicardial ectomy prevented massive myocardial infarction in all animals.

The simple omental graft without pedicle operation protected 40 per cent of the animals from massive myocardial infarction.

When epicardiectomy, zero-pericardiectomy and omental graft were performed 5 (25 per cent) had no infarction and 10

(50 per cent) had scattered foci of fibrosis; none of the 75 per cent survivors had moderate to massive infarction.

In the last series in which epicardiectomy, zero-pericardiectomy, omental graft and internal mammary artery implant were performed 11 of 14 animals survived. 7 of these (50 per cent) showed no myocardial infarction in either ventricle and 4 (36 per cent) showed only scattered

foci of fibrosis. None of the 11 surviving animals showed any evidence of moderately severe or massive myocardial infarction. All implants were patent. The average internal mammary artery patency for surviving animals was 71.8 per cent.

In Table II we have attempted to summarize our pathologic studies after triple coronary artery occlusion in all seven animal series. There is clearly a great difference in right and left ventricular muscle mass damage between the control and the treated animal in the last two groups.

The last two operations, namely epicardiotomy, aorto-pericardiotomy and the free omental graft alone or combined with internal mammary artery implantation operation were the only two procedures after which the animals had not only a

high survival rate as shown in Table I but also a high survival rate of the ventricular muscle masses of both ventricles as shown in Table III.

Injection studies. The close correlation between animal survival after triple coronary artery occlusion and the development of extracardiac coronary anastomoses may be seen in the tabulation of coronary artery anastomoses shown in Table IV. In this table the various anastomoses which developed are shown for those animal which died spontaneously and for those which were sacrificed for study. Anastomoses have been graded as follows: 0 Slight anastomoses + Moderate anastomoses ++ Extensive anastomoses +++.

EXTRACARDIAC CORONARY ANASTOMOSES

Table IV. Tabulation of coronary extracardiac and mammary coronary anastomoses after triple coronary artery occlusion and revascularization surgery

	Number of animals in series	Animals dying spontaneously						Animals sacrificed							
		Number of animals	Extra cardiac anastomoses		Intercoronary		Intra-coronary		Number of sacrificed animals	Extracardiac anastomoses		Intercoronary		Intra-coronary	
			+++	++	+++	++	+++	++		+++	++	+++	++	+++	++
Control	90	0	0	0	0	4	0	5	—	—	—	—	—	—	—
Treated															
1 Epicardiotomy	10	9	0	0	0			7	1	0	0	1	0	1	0
2 Epicardiotomy and aorto-pericardiotomy	10	8	0	0	0		4	4	9	0	0	0	0	2	0
3 Epicardiotomy and internal mammary artery implant	10	6	0	0	0	1	1	3	4	0	0	1	1	4	0
				1M						1M	1M				
4 Free omental graft	10	6	1	0	0	0	0	0	4	9		3	1	4	0
5 Epicardiotomy aorto-pericardiotomy and free omental graft	0	3	0	1	0	1		3	15	4	11	5	9	11	4
6 Epicardiotomy aorto-pericardiotomy free omental graft and internal mammary artery implant	14	1	0	1	0	0	0	3	11	7 plus 1M	4 plus 1M	5	6	9	
				1M											

1M Internal mammary artery anastomoses +++ Extensive anastomoses ++ Moderate + Slight

Of the total of 94 animals (20 controls and 74 treated) 57 animals died spontaneously all within an average of 24 days. 14 showed no extracardiac anastomoses (Fig. 2). Thirty-seven of the 74 treated animals survived and were sacrificed for study.

13 of these showed extensive and 17 moderate extracardiac coronary anastomoses not including mammary coronary anastomoses.

In Series 4 in which the free omental graft was simply wrapped around the heart



Fig. 2 Roentgenogram of the heart of Animal No. 208 which died after triple coronary artery occlusion by Ameroselectin. The animal was killed 19 days after surgery. The only injection made was through the thoracic aorta. In this animal, 54 of 57 animals which died spontaneously there was no evidence of the development of extracardiac coronary anastomoses.

and the pericardium closed it was possible to fill the coronary arteries with injection mass through the aorta via the graft (Fig. 3).

In Series 5 in which only epicardiectomy and free omental graft were performed 15 of 20 animals survived and 15 had moder-

ate to extensive extracardiac coronary anastomoses (Fig. 4).

The anastomoses referred to are those that form between the mediastinal vessels, pericardium, omentum and coronary arterioles. These are quite apart from the



Fig. 3. Roentgenogram of the heart of Animal No. 131, which died from a massive myocardial infarction in the right ventricle 35 days after placement of triple coronary artery Ameroids and a free omental graft. The only injection made was that through the thoracic aorta. The extracardiac radiopaque injection showed the development of omental mammary-coronary anastomoses bringing the dye into the left coronary arterial system.

anastomoses formed between the implanted internal mammary artery and the myocardial arterioles (Fig. 5). The latter are listed as separate anastomoses in Table IV; thus in the two implant series there are anastomoses not only from the

supplementary operative procedures but from the internal mammary artery itself.

INTERNAL MAMMARY ARTERY IMPLANT WITH SUPPLEMENTARY OPERATIONS In Series 3 in which the internal mammary artery was combined with epicardectomy, there



Fig. 4. Roentgenogram of the heart of Animal No. 487 which survived triple coronary artery Ameroid occlusion, epicardectomy, and free omental graft operation. The animal was sacrificed and studied 469 days after surgery. The only injection made was that through the thoracic aorta. In this animal the injection mass filled the coronary arterial tree via the mediastinal-omental, omental-coronary, and omental myocardial anastomoses.



Fig. 5. Roentgenogram of the heart of Animal No. 949 which had survived triple coronary artery occlusion by Ameroid, internal mammary artery implantation and free omental graft. The animal was studied 12 months after surgery. The only injection made was that through the thoracic aorta. In this animal the injection mass not only filled the coronary arterial tree via the mediastinal omental coronary and myocardial vessels but filled the internal mammary artery in retrograde manner as well.

were 6 patent mammary coronary anastomoses. Two of these animals died in these extensive intercoronary anastomoses had failed to form. In the 4 animals which survived there were extensive and moderate intercoronary anastomoses. When the omental graft was added to the internal mammary artery 12 of 14 internal mammary arteries were patent. 11 of the animals survived and these showed moderate to extensive mammary coronary anastomoses. The internal mammary artery mammary coronary anastomoses were in addition to moderate and extensive extracardiac mediastinal coronary anastomoses which had been formed as a result of the free omental graft.

INTERCORONARY ANASTOMOSES In none of the animals which died spontaneously either the control or the treated groups was there a single one which showed extensive intercoronary anastomoses (Fig. 6). On the right hand side of Table IV the findings in the animals which were sacrificed for study are recorded. Of the 37 animals which survived and were

sacrificed for study there were 19 which showed extensive and 17 that showed moderate intercoronary anastomoses (Fig. 7).

Discussion and conclusion

The triple coronary artery Ameroid constriction test offers a reliable method of achieving a revascularization procedure. This simple test causes 100 per cent mortality in animals. There was massive myocardial damage in 17 of the control animals. A study of extracardiac coronary anastomoses and intercoronary anastomoses showed that nature failed to develop extracardiac coronary anastomoses. Likewise nature failed to develop extensive intercoronary anastomoses. The most that nature was capable of doing in response to occlusion of all three coronary arteries was to develop moderate intercoronary anastomoses.

Epicardiectomy and free omental graft proved to be effective in preventing death of the animal (75 per cent survival). It was likewise effective in protecting the



Fig. 6. Ventral view of the heart of Animal No. 14 which died 117 days after triple coronary artery constriction. The right coronary artery and then the left coronary artery were injected with 5 ml. of heart wax. The heart was sacrificed. It was noted that the almost complete absence of intercoronary anastomoses.

ventral view
The

Cardiomegaly in myxedema

Report of a case and review of the literature

Edwin W. Monroe MD*

Eric L. Iearrington MD

Greenville NC

Clinical and pathologic descriptions of cardiac abnormalities in myxedema have appeared in the medical literature for more than three quarters of a century. These began with a comprehensive review of myxedema by the Clinical Society of London in 1888.¹ The autopsy findings in 20 myxedematous patients were studied including an examination of the heart in 9 cases. Two of these nine hearts were described as showing definite pathologic change—interstitial myocarditis. The concept of myxedematous heart disease as a distinct entity was initiated by Zondek in 1918 and defined more completely by Fahr² in 1925. Both authors observed and described dilated hearts, slow pulse rates, normal blood pressures and low voltage on electrocardiograms in markedly myxedematous patients. These cardiac abnormalities demonstrated essentially a complete reversal to normal after treatment with thyroid.

Since those early attempts to define the cardiac status in myxedema this matter has been the object of numerous case reports and periodic reviews. Many of these articles imply that myxedematous pericardial effusion is the sole cause of the clinical picture of myxedema heart—including the electrocardiographic and chest roentgenographic abnormalities. The pur-

pose of this article is to present the case of a patient with massive cardiomegaly and pericardial effusion who probably also demonstrates primary involvement of the myocardium in severe myxedema. The literature as it pertains to cardiomegaly in myxedema is reviewed in order to re-examine the role played by pericardial effusion.

Case report

E. G., 55 year old Negro woman was admitted to Pitt County Memorial Hospital for the first time on Sept. 7, 1967. A survey fluoroscopy roentgenogram recorded 17 years previously had shown that her heart was enlarged. Fifteen years before admission she began to complain of mild dyspnea, orthopnea and pedal edema. She was placed on digitalis which she continued to take regularly. For 2 years prior to admission her dyspnea and edema progressed rapidly in spite of diuretics, orally and by parenteral injection. For 17 years she had been aware of some fullness in the lower anterior region of the neck. She described drainage of her skin, partial alopecia, hoarseness, sluggish constipation, intolerance to cold and loss of memory—all of these symptoms had progressed slowly over the past 15 years. She had been pregnant on one occasion 21 years previously with a normal delivery, this had been followed by normal meneses until 17 years ago when her menses stopped spontaneously at age 38. A gradual loss of weight of 30 pounds had occurred during the 15 years before this admission to hospital. A close friend of hers was known to have pulmonary tuberculosis. There was no history of angina, hypertension, renal disease, cough, fever or night sweats.

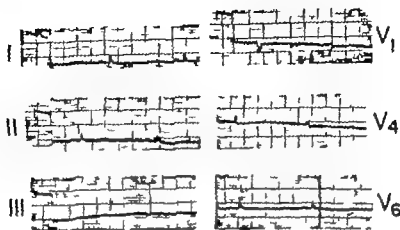


Fig 1 Electrocardiogram recorded Sept 10 196 before treatment.

The physical examination on admission revealed an oral temperature of 99.8°F , pulse of 50 per minute and blood pressure of 140/86 mm Hg. No paradoxical pulse was found. She was short (59 inches) plump (125 pounds) and pleasant but rather somnolent. Mild orthopnea was apparent. The skin was very dry and itching; the hair was coarse and dry and there was partial alopecia of the scalp. The tongue seemed to be slightly enlarged. The neck veins were flat. The thyroid gland was slightly enlarged; no nodularity was noted. The lungs were clear to percussion and auscultation. The cardiac examination revealed a barely palpable point of maximal impulse on the fifth left intercostal space 8 cm from the mid sternal line; later as the left border of cardiac dullness extended into the left axilla. A_2 was louder than P_2 . A third or fourth systolic murmur was heard in the second right anterior intercostal space posteriorly; no gallop or rub was detected. The liver and spleen were not palpable. Moderate pitting edema was noted in the pretibial and pedal areas. No bruits were present over the abdominal aorta or the peripheral arteries. Her speech was slow and her voice was hoarse; her attention span was brief. The deep tendon reflexes exhibited a markedly prolonged relaxation phase.

Laboratory data included a negative VDRL, hemoglobin 8 Gm per cent with the red blood cell described as normocytic and normochromic on the peripheral blood smear; white blood count 4000 with a normal differential count; urinalysis revealed specific gravity of 1010 with one plus albumin; fasting blood sugar 92 mg per cent; blood serum sodium 112 mg per cent; serum sodium 130 mEq per liter and serum potassium 4 mEq per liter; serum albumin 2.9 Gm per cent and serum globulin 2.1 Gm per cent. The basal metabolic rate was -26 per cent. A serum cholesterol was 350 mg per cent (normal in this laboratory 140 to 250 mg per cent). The serum protein bound iodine is reported to be 0.7 μg per cent. A 24 hour collection of urine for follicle stimulating hormone content is reported to be normal. An electrocardiogram

revealed a normal sinus rhythm at 45 per minute with P-R-T interval second Q-T 0.06 second and Q-T not measurable because of anelectric T wave throughout the Q-TS voltage was very low (see Fig 1). The chest x-ray film showed a massively enlarged cardiac silhouette with no apparent pulmonary congestion (see Fig 2).

Course in the hospital. The patient was thought to have myxedematous heart disease with pericardial effusion. She continued on 0.1 gm of digitoxin daily and a 700-mg sodium diet. Because of the possibility of the presence of atherosclerotic coronary artery disease thyroid extract was started 15 mg with an initial dosage of 10 mg daily. This was cautiously increased to 64 mg daily over the ensuing 4 weeks. At this point her objective ex-

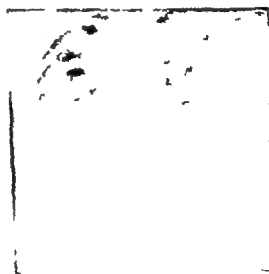


Fig 2 Chest x-ray film recorded Sept 10 196 before treatment.



Fig 3 Chest x-ray film dated Oct 3 1962—upright—after pericardiocentesis and inflation of air into the pericardial sac.

plaint of dyspnea had improved, she had lost 6 pounds and had no edema. A repeat PBI was 2.1 μ g per cent. However, chest x-ray film showed that the cardiac silhouette was unchanged. A pericardiocentesis was performed on Oct 3 1962 with the removal of 1,700 c.c. of turbid yellow fluid which did not clot. This fluid was negative on routine and acid fast culture and had a cholesterol content of 360 mg per cent and a protein content of 790 mg per cent. Toward the end of the pericardiocentesis 300 c.c. of air was introduced into the pericardial sac. A best x-ray obtained thereafter demonstrated that the massive cardiomegaly was due almost totally to the air quantity of pericardial fluid; the pericardium was noted to be quite thin and the heart per se was probably normal in size (see Fig 3). On Oct 12 1962 another pericardiocentesis yielded 450 c.c. of pink tinged yellow fluid. The overall size of the cardiac silhouette was unchanged by the removal of this total of 1,650 c.c. of pericardial fluid. However, the patient noted marked improvement in her general state of well-being and was allowed to go home on a regimen of 64 mg of thioridazine extract daily, 0.1 mg of digoxin daily and a 200-mg sodium diet. Two weeks later she complained of increasing dyspnea and a dull constant aching discomfort in the anterior chest; a low grade fever was present. She was readmitted to Fort County Memorial Hospital on Nov 16 1962 and remained there for 1 week. Her temperature curve showed a daily spike of 101 F orally. The hemoglobin was 9 Gm per cent and the white blood count was 6,250 with a normal differential. A PBI was 4.4 μ g per cent. The electrocardiogram showed improved QRS and T₁ voltage with a sinus rate of 85 per minute; no injury pattern was present. A chest x-ray film indicated that the massive cardiac silhouette was unchanged and no pulmonary infiltration was apparent. Because of the fever and a positive old tuberculin skin test in a 1:1000 dilu-

tion in this patient with continued massive pericardial effusion whose clinical myxedema had improved markedly, she was transferred to Grady Sanatorium Chapel Hill N.C. on Nov 23 1962. The presumptive discharge diagnosis was possible tuberculous pericarditis and myxedematous heart disease with pericardial effusion.

Summary of Grady Sanatorium admission. The patient was admitted on Nov 23 1962 and discharged on Jan 24 1963. The history was that outlined above. The physical examination revealed normal vital signs with a small goiter and mild continued evidence of myxedema. This was manifested by dry and scaly skin with dry brittle hair and slight alopecia of the scalp; the voice was husky; the deep tendon reflexes continued to demonstrate a rather prolonged relaxation phase. The lungs were clear and no edema or hepatomegaly was present. The left border of cardiac dullness extended into the left axilla and the point of maximal impulse could not be located. The previously described aortic systolic murmur was unchanged. A pericardial rub was not present.

A summary of pertinent laboratory data included hematocrit 26 per cent on admission and 37 per cent on discharge; WBC 6,150 with a normal differential; a normal urinalysis; the blood urea nitrogen serum electrolytes serum proteins and liver function studies were normal. LF cell preparations were negative as were sputum studies and gastric washings for acid fast bacilli and for fungi. An electrocardiogram on admission was similar to one obtained 12 days earlier during her second admission to the local hospital. A chest x-ray film continued to demonstrate massive cardiomegaly and cardiac fluoroscopy revealed only feeble palpation of the heart borders.

Course at Grady Sanatorium. The patient was



Fig 4 Angiocardiogram dated Jan 11 1963 demonstrating that continued cardiomegaly is now due to left ventricular enlargement.

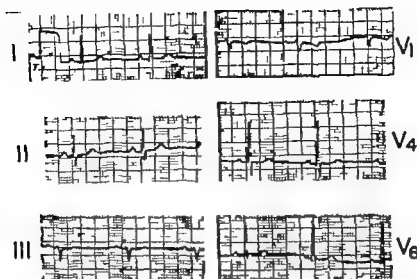


Fig 5 Electrocardiogram dated Nov 28 1964. This indicates virtually a complete return to normal



Fig 6 Chest x ray film dated Dec 5 1964 demonstrating the reversal to a normal cardiac silhouette

continued on salt restriction and 0.1 mg. of digoxin daily. She was placed on osmotic acid hydrazide and perimonomelic acid as a therapeutic trial and as prophylaxis during her stay in the sanatorium. The dosage of thyroid extract was increased to 170 mg. daily. The butane-extractable iodine was 2.6 µg per cent on admission and rose to 4.5 µg per cent during her 2 month stay in the sanatorium. Three days after admission 600 c.c. of pink tinged yellow fluid was obtained by per-

cardiocentesis. This fluid was sterile on culture and showed no abnormal cells. Several venous pressures and circulation times were normal. The low grade fever disappeared during her first 2 weeks of hospitalization as did all of her subjective complaints. However repeated chest x ray films showed no diminution in the size of the cardiac silhouette even though her thyroid status seemed to be normal clinically and by BEI measurement and the electrocardiogram demonstrated marked improvement in the shape of the QRS and T waves. A second pericardiocentesis was attempted on Jan 9 1963 and only 10 c.c. of fluid could be obtained. Therefore a second aortogram was obtained (see Fig 4). This demonstrated little if any residual pericardial fluid and delineated a markedly dilated heart—especially the left ventricle. It was postulated that the continued cardiomegaly was due to myxedematous myocardopathy. The patient was removed from antitubercular therapy and discharged on digoxin 0.1 mg. daily thyroid extract 120 mg. daily and a low salt diet.

Since discharge from Grady Sanatorium on Jan 24 1963 the patient has been seen at regular intervals. In July 1963 she seemed to be mildly hyperthyroid also complained of nervousness and pounding heartbeat and her PBI was 7.6 µg per cent. The thyroid dosage was reduced to 90 mg. daily. Since then she has remained well gradually resumed household activity and has been told by old friends that she appears to be years younger. Over the past 7 years she has gained 25 pounds to a current weight of 136 pounds and her alopecia and other integumentary abnormalities have been completely corrected. The PBI has ranged between 5 and 6 µg per cent. The electrocardiogram has remained normal (see Fig 5). The enlarged cardiac silhouette has gradually returned to almost normal size. A chest x ray film dated Dec 5 1964 showed a cardiothoracic ratio of 13.2–24.2 cm (see Fig 6). She has had no cardiac symptoms but the aortic

as to the murmur is unchanged and is thought to represent a symptomatic atherosclerotic involvement of the aortic valve.

Review and discussion of literature

In 1949 Kern and associates⁴ described pericardial effusion as being a constant early and major factor in the myxedematous heart. Four patients were reported with myxedematous pericardial effusions and the authors stated that the resultant cardiac syndrome was due solely to the effusion and not contributed to by any myocardial change. They described the cardiac silhouette on chest roentgenogram and the electrocardiographic changes to the presence of pericardial fluid and concluded that the heart itself was not enlarged or involved. Schnitzer and Cutmann⁵ had reached the same conclusions 3 years earlier when they reviewed the literature and added their report to illustrate how commonly pericardial effusion is found in myxedematous hearts. This report also demonstrated that treatment with thyroid will cause the electrocardiographic and chest x-ray changes to revert to normal. In 1953 Marks and Roof⁶ reviewed 14 reported cases of myxedematous pericardial effusions and added 2 of their own. Both patients had large effusions but were not in congestive heart failure. These authors concluded that the pericardial effusion as well as the less commonly found pleural and peritoneal effusions were not due to primary myocardial insufficiency since they responded so well to thyroid therapy alone.

The general subject of the heart in myxedema was reviewed in 1961 by Himelstik⁷ and Levine and associates.⁸ Both of these articles stressed the frequency with which pericardial effusions are found in the myxedematous heart and attributed the electrocardiographic abnormalities (low voltage flat or inverted T waves and occasional conduction defects) to the presence of the pericardial fluid. The electrocardiographic changes were observed to improve after pericardiocentesis. These authors also concluded that the roentgenographic finding of an enlarged cardiac silhouette was due to the pericardial effusion. The similarity of the clinical picture to that of congestive heart

failure was discussed with the following differences noted: (1) the myxedematous patients had normal venous pressures and only rarely any evidence of lung congestion; (2) the pericardial fluid in myxedematous had a high protein content whereas the fluid of heart failure is low in protein; (3) digitalis does not improve the status of the myxedematous heart but thyroid will cause it to revert to normal.⁹

The pathophysiologic derangements responsible for the collection of fluid in the serous cavities of a markedly myxedematous patient are poorly defined. A greatly increased capillary permeability has been found in such patients by Lange.¹⁰ Renal clearance studies by Young and Little¹¹ delineated a decrease in glomerular filtration renal plasma flow and renal blood flow but the capacity of the patient with myxedema to excrete salt and water was noted to be normal. Hemodynamic studies by Scheinberg and associates¹² and by Crutinger and co-workers¹³ demonstrated a low cardiac output in myxedematous patients. However these studies also showed that oxygen consumption was low and thus the A-V oxygen difference at rest and with exercise was not relatively widened thus indicating that flow was proportional to the oxygen demands of the body. This contrasts with congestive failure in which along with a decreased cardiac output the A-V oxygen difference is great—indicating more extraction of oxygen by the tissues per unit of blood flow thereby compensating for the reduced flow. Ellis and associates¹⁴ studied the hemodynamics of 5 myxedematous patients and found the cardiac output to be decreased and parallel to the decrease in oxygen consumption. Three of his patients had no increase in end diastolic pressure such as is seen in heart failure and the cardiac output increased with exercise—again differing from the response in heart failure. McBrien and Hinkle¹⁵ noted that the cardiac output decreased in 19 of 20 patients with myxedema during the Valsalva maneuver—similar to the response in a healthy heart—but no reflex slowing of the rate occurred such as has been found to occur in the healthy heart. The other patient showed a heart failure response with no fall in pulse pressure

during the Valentin maneuver this patient was noted to be in overt congestive failure.

Descriptions of specific pathologic changes in the hearts of myxedematous patients are lacking. Various authors have described autopsy findings but these add little to the description of nonspecific myocarditis changes noted in 1938.¹ Since most of the patients dying with myxedema are elderly, many of the pathologic changes are contributed to by the aging process. Thus the fibrous tissue replacement in the myocardium noted by Brewer¹² and by Douglas and Jacobson¹³ is also described in patients with progressive coronary artery disease. In myxedema the heart itself has been found to be pale, flabby, and dilated. There is interstitial edema in the myocardium which is seen microscopically as a faint, basophilic substance that is brilliant Papanicolaou stain, high in protein and thought by Brewer¹² to be similar to the mucopolysaccharide of the ground substance. Goldberg¹⁴ performed thyroidectomies on sheep and goats and at autopsy 2 years later found pericardial effusions surrounding hearts that were pale and flabby with microscopic disintegration of muscle fibers. In spite of these occasional reports of myocardial abnormalities noted in autopsied hearts, the impression persists in the literature that all of the ailing facts point to pericardial effusion as the factor primarily responsible for the clinical picture of the myxedematous heart.¹⁵

The ability of the chest roentgenogram and the electrocardiogram to determine whether abnormalities in these ancillary parameters of clinical evaluation were due solely to myxedema was explored by Aber and Thompson.¹⁶ They evaluated 33 patients with clinical myxedema. Twenty-seven of these had electrocardiographic changes typical of myxedematous heart disease—low voltage and flat or inverted T waves. In the other 26 patients the electrocardiographic findings were not suggestive of myxedematous heart disease—15 had normal tracings, 11 had only very slight changes, 7 had a left bundle branch block, 2 had left ventricular hypertrophy, and 6 had evidence of severe coronary artery disease. The chest x-ray films of almost all of these same 26 patients

showed an enlarged cardiac silhouette. In the 27 patients with electrocardiographic evidence of myxedema chest x-ray films showed an enlarged cardiac silhouette in 14 and a normal heart size in the other 13. The authors concluded that the combination of an enlarged cardiac silhouette on chest x-ray films and an abnormal electrocardiogram implicated some underlying or associated cardiac disease in addition to clinical myxedema. Another tentative conclusion or interpretation could be reached on the basis of this study—at least one half of the patients with myxedema will have an enlarged cardiac silhouette on chest x-ray films along with an electrocardiogram showing typical changes of myxedema. And if the heart is enlarged on the x-ray film and the electrocardiogram does not show classic myxedematous change, some other cardiac disease should be suspected as the cause for the enlargement.

As mentioned earlier, many patients with myxedema have a sclerotic coronary artery disease.^{7,16,17} However, angina pectoris is not a common symptom of untreated myxedema and if present it may disappear or improve with cautious thyroid replacement. Conversely, aggressive thyroid replacement may precipitate angina, especially in elderly myxedematous patients.¹⁸ The entire concept of adult myxedema and its treatment by hypercholesterolemia and its attendant hypercholesterolemia are predicated to premature or untreated atherosclerosis is open to critical reevaluation and clarification.¹⁹ A typical example of this presumed relationship is found in the autopsy series of Douglas and Jacobson,¹³ wherein coronary atherosclerosis was noted to a significant degree in all 10 cases of myxedema. However, the ages of the patients ranged from 67 to 78 years—ages at which coronary disease is prevalent even without myxedema.

The problem of discerning the presence of congestive failure in the patient with marked myxedema is a very real one, especially when one is confronted by peripheral edema, ascites, pleural effusion, marked cardiac enlargement on the chest x-ray film and an electrocardiogram that shows broad waves and very low voltage with widespread T wave flattening, or inversion. This patient frequently is quite

dyspneic and orthopneic. If the venous pressure is normal and the chest x-ray film shows little or no pulmonary congestion the physician can afford to begin thyroid replacement cautiously and observe the response. However, many clinicians feel obliged to reassure themselves that they are not dealing with an associated disease such as tuberculous pericarditis, pericardial effusion due to malignancy, etc. A pericardiocentesis can be performed with very little risk to the patient. If the fluid has a high content of protein and cholesterol and generally fits the criteria established for effusions in myxedema⁴⁷ then watchful waiting to observe the response to thyroid therapy can be pursued. The negative reports from the acid fast studies and cell blocks on the fluid reinforces the observant attitude.

Fortunately, the patient described in this case report represents a minority of the large group of myxedematous patients encountered in medical practice. However, it is a difficult minority to evaluate and manage. In such patients angiocardigraphy can be quite helpful in defining cardiomegaly—as shown by Kuttredge and Yasocrites⁴⁸ and by the patient described in this case report. Newer techniques of evaluating cardiomegaly are being developed such as gas injection⁴⁹ radio-active isotope scanning⁵⁰ and ultrasound⁵¹

Comments and summary

The case of a patient with long standing, severe myxedema including myxedematous heart disease is presented. Two salient features are to be noted in this case report: (1) the massive cardiomegaly which was mutually demonstrated to be due to a vast quantity of pericardial fluid and (2) continued massive cardiomegaly after all of the pericardial fluid had been removed or had resolved. The cardiac silhouette at this point was demonstrated by angiocardigraphy to be due primarily to left ventricular dilatation.

The literature pertaining to cardiomegaly in myxedema is reviewed and discussed. The trend in the literature of ascribing all of the features of myxedematous heart disease to pericardial effusion is questioned. Primary myocardial involvement in severe myxedematous heart disease would seem

to have some role in the cardiomegaly of such patients.

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The occurrence and mechanism of P-wave inversion in Lead I in right atrial overloading

Report of two cases

U Mironski MD

I Yure MRC S (Eng) L R C P (Iond)

Zefim Israel

Classically inverted I waves in Lead I have been considered to be the most specific electrocardiographic sign of mirror image dextrocardia. Today this concept is no longer justified. It has been shown that due to left atrial rhythm, upright I waves in Lead I appear frequently in mirror image dextrocardia, whereas inverted I waves in this lead may be observed in patients with normally placed hearts.¹ Moreover it has been postulated that inverted I waves in Lead I may also occur as a result of marked right atrial hypertrophy or dilatation² or in nodal rhythms.

Since the presence of negative P waves in Lead I in right atrial hypertrophy is not well documented in the literature we thought it to be worth while to report 2 such cases. These observations are of particular interest because they provide convincing evidence of the causal relationship between the degree of right atrial overloading, and the polarity of the P waves in Lead I. An explanation concerning the mechanism of this finding will be suggested.

In the electrocardiographic context of this report the terms right atrial hypertrophy, dilatation, and overloading, will be used interchangeably.

Case reports

Case 1 A 32 year old boy was admitted to the pediatric department because he had had recurrent attacks of bronchial asthma for the previous few years. Between attacks the clinical picture was characterized by moderate pulmonary emphysema. A 12 lead electrocardiogram recorded during a quiescent period (Fig. 1) showed signs of right atrial hypertrophy. The I wave was inverted and peaked in Leads II, III and aVF recording, in amplitude of almost 7.5 mm. The I wave was upright in Lead I. The frontal I and QRS axes were +75 and +50 degrees respectively.

(Fig. 2) a 12 lead electrocardiogram recorded during an attack of asthma. The signs of right atrial overloading were negative. The most pronounced thus previously noted I wave was in Lead II, III and aVF having an amplitude of almost 3.5 mm. The I wave in Lead I became flat with the second part of it slightly inverted. Both the frontal I and QRS axes shifted to the right (+100 and +70 degrees respectively).

Case 2 A 77 year old man was admitted to the surgical department for prostaticectomy. His past history was unremarkable except for the fact that he had suffered for years from bronchopneumonia and thrombosis. The clinical examination confirmed the presence of chronic lung disease. A routine electrocardiogram reproduced in the upper two rows of Fig. 3 showed evidence of right atrial hypertrophy with tall and peaked I wave having an amplitude of 3 mm in Leads II, III and aVF. The I waves in Lead I were slightly inverted. The possibility of concern that left atrial enlargement is suggested by the negative I wave in Lead I. The mean I and QRS axes were directed in the 1st and 2nd of the +100 degree position in the frontal plane.

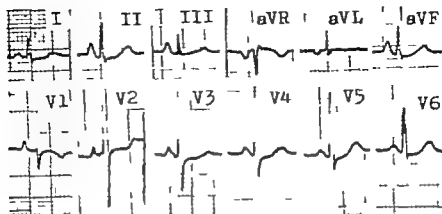


Fig. 1 Electrocardiogram of Case 1 showing presence of right atrial overloading. The P waves in Lead I are upright.

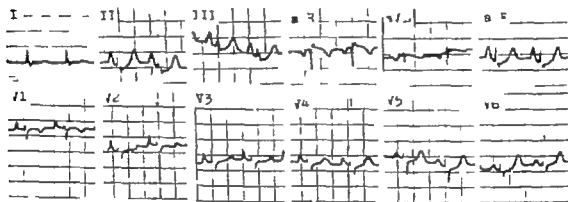


Fig. 2 Electrocardiogram of Case 1 taken during an attack of bronchial asthma. The P waves in Lead I have now become flat with their second part slightly inverted, whereas in Leads II, III and aVF they are taller than they were in Fig. 1.

In the bottom row of Fig. 3 are reproduced the limb leads recorded during a period when the patient's respiratory difficulties were particularly pronounced. The electrocardiographic evidence of right atrial overloading is now much less pronounced as demonstrated by the decreased amplitude of the P waves in Leads II, III and aVF. Simultaneously the P waves in Lead I became upright.

Discussion

Although the P waves in right atrial overloading are usually tall and peaked in Lead II, III and aVF they are of small amplitude in Lead I and occasionally may even become isoelectric.⁸ Such changes are related to the increased magnitude and to a shift to the right of the resultant atrial vectors. It is accepted that this

right deviation of the mean P vector is moderate and almost never exceeds the +90 degree position in the frontal plane.⁸ A phenomenon which explains the usual absence of negative I waves in such cases. The fact that inverted I waves in Lead I do appear occasionally in right atrial overloading is evident from this communication.

In the cases presented above the other possible cause of I wave inversion in Lead I was eliminated. Obviously there was no mirror image dextrocardia. Left atrial rhythm was excluded by analysis of the precordial leads which showed upright I waves over the left precordium.¹ The absence of retrograde P waves in the

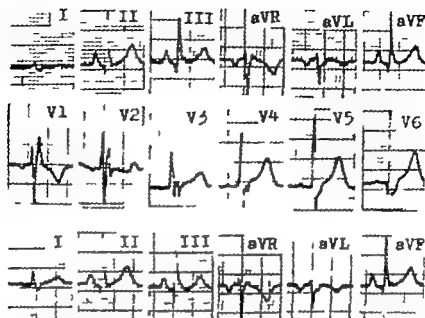


Fig 3 Electrocardiogram of Case 2. *Upper two rows:* Note the slightly inverted I wave in Lead I and evidence of right atrial overloading. *Bottom row:* Limb leads recorded during a period of quiescence of the patient's respiratory chain. Note the upright P wave in Lead I. The I waves in Leads II, III, and aVF are not so tall nor so peaked as previously.

limb leads eliminated a nodal arrhythmia.

On the other hand it is clearly demonstrated in our patients that an increase in right atrial overloading is accompanied by a flattening or even an inversion of the P waves in Lead I whereas a decrease in stress on the right side of the heart is followed by a rise in the P waves to their original position.

It appears that the basic mechanism responsible for such changes is of a positional rather than a structural nature. This is indicated by the moderate shift of the mean P vector to the right by the fact that such a shift is accompanied by a corresponding deviation of the QRS axis and mainly by the transitory and reversible character of the electrocardiographic changes.

In order to explain the inversion of P waves in Lead I in right atrial overloading it is not necessary to assume a shift of the mean P vector beyond the +90-degree position in the frontal plane. Such an assumption would be justified if the axis of Lead I were exactly horizontal as postulated by Einthoven's equilateral triangle hypothesis. It is well known, however,

that Einthoven's triangle does not represent accurately the anatomy and electrophysiologic facts and that the actual triangle is scalene rather than equilateral.¹¹ In this scalene or Burger's triangle the effective axis of Lead I is oblique with a more or less pronounced inclination from the horizontal according to individual variations. Thus a relatively moderate deviation of the P vector to the right for example from an average +30 degree position to a +75 degree position may lead to a projection of this vector on the negative half of the effective Lead I axis and consequently to an inscription of inverted P waves in this lead (Fig. 4).

This explanation is supported by an analysis of the precordial leads. A deviation of the mean I vector beyond the +90-degree position means a change from the average right-to-left direction of activation to a left-to-right one and implies a simultaneous inversion of the I waves in Lead V₆, a lead similar to Lead I in its response to the transverse component of the dipole vector.¹² In our cases, however, the polarity of the P waves in Lead V₆ remained unchanged whereas the P waves

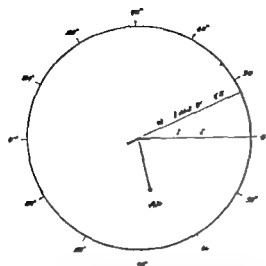


Fig. 4. A diagram demonstrating that a P vector located in the vicinity of $+75$ or $+80$ degrees may be projected on the negative half of the effective (Berger) Lead I axis thus giving rise to inverted P wave in the lead. For further explanations see text.

in Lead I became inverted a phenomenon that is best explained by an obliquity of the Lead I axis as represented diagrammatically in Fig. 4.

The above presented explanation seems to be valid for both patients in spite of their widely different ages and in spite of the fact that the electrocardiogram of the second patient suggests other abnormalities such as left atrial enlargement and right bundle branch block.

Summary

Two cases of P wave inversion in Lead I due to right atrial overloading have been described. It was demonstrated that the polarity of the P wave in Lead I is directly related to the degree of overloading on the right side of the heart.

It was postulated that the negativity of the P waves in Lead I in right atrial overloading does not necessarily express a shift of the mean P vector beyond the $+90$ degree position in the frontal plane. Because of the usual inclination of the effective Lead I axis from the horizontal in the Burger triangle a deviation of this vector to the right even though it still is less than $+90$ degrees may give rise to inverted P waves in Lead I.

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Origin of the right pulmonary artery from the aorta

Harvey S. Rosenberg, M.D.*

Grady L. Hallman, M.D.**

Robert R. Wolfe, M.D.***

Joseph R. Laison, M.D.****

Houston, Tex.

The right pulmonary artery may arise from the aorta as a result of at least two different mechanisms. In Type I (Fig. 1A) the proximal portion of the right aortic arch is absent and the distal portion persists as a right ductus arteriosus forming a communication between the distal portion of the pulmonary artery and the innominate artery. In Type II (Fig. 1C) a displaced septum in the embryonal truncus arteriosus results in an aortic origin of the right pulmonary artery near the base of the heart.

In both types of abnormal origin of the right pulmonary artery, the left lung is exposed to the entire output of the right ventricle if the intracardiac structure is normal. With loss of the proximal portion of the aortic arch (Type I) the communication with the distal portion of the pulmonary artery through a right ductus arteriosus is small, resulting in a decreased flow of blood to and presumably a decreased pressure in the right lung. When the embryonal truncal septum is displaced (Type II) circulation to the right lung is

unimpeded and the lung is exposed to systemic pressures.

Structural changes in the small pulmonary arteries result from both increased flow of blood and increased pressure. When the right pulmonary artery arises from the aorta and the left pulmonary artery pursues its normal course, the left lung is perfused with the entire output of the right ventricle at increased pressure, whereas the right lung is perfused with a normal or low flow at systemic pressure. In either type of defect, the left lung is exposed to high pressure at high flow, and the right lung is exposed to normal or decreased flow at high or low pressure.

Case reports

Case 1. The patient, a critically ill 7 week old white male infant, was hospitalized on May 7, 1963 with cyanosis, respiratory distress of 2 weeks duration, poor feeding, and diarrhea of 3 days.

Physical examination revealed severe respiratory distress, slight cyanosis, and 10 per cent dehydration. He had a weak cry and responded poorly to stimuli. He weighed 8 pounds and 5 ounces and his temperature was 94 F. Axillary and brachial pulses were present. Mucous membranes were dry. Sub-

From the Departments of Pathology, Surgery, and Pediatrics, Children's Hospital, University of Texas Medical Branch at Houston, Texas.

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Address correspondence to Dr. Harvey S. Rosenberg, Children's Hospital, University of Texas Medical Branch at Houston, P.O. Box 30088, Houston, Texas 77030.

*Assistant Professor of Pathology, Children's Hospital, University of Texas Medical Branch at Houston, Texas.

**Resident, Pediatrics, Children's Hospital, University of Texas Medical Branch at Houston, Texas.

***Resident, Cardiac Laboratory, Children's Hospital, University of Texas Medical Branch at Houston, Texas.

****Resident, Cardiac Laboratory, Children's Hospital, University of Texas Medical Branch at Houston, Texas.

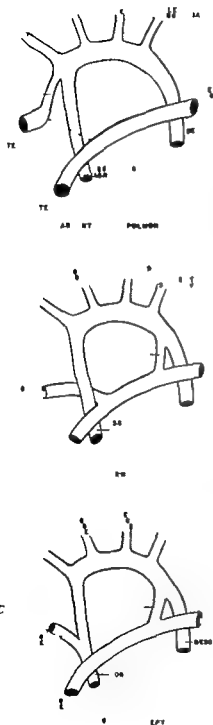


FIG. 1. Diagrams of the relationship of the pulmonary arteries and the aorta. *A* Right patent ductus arteriosus and absent right pulmonary artery (Type I defect). *B* Normal. *C* Anomalous septation of the truncus (Type II defect).

costal and subcostal retractions accompanied respiration. On auscultation of the lungs in my crepitant rales were heard especially on the left. The right ventricle was over-sized and a Grade 2 (out of 4) short mid systolic ejection murmur was heard along the left sternal border. The second pulmonary sound was narrowly split and louder than normal. The liver was 5 cm below the right costal margin.

Röntgenogram of the chest showed marked cardiac enlargement and congested lungs. An electrocardiogram revealed right axis deviation, right atrial enlargement, right ventricular hypertrophy and sinus tachycardia.

The patient was treated for heart failure with bumetide C for dehydration with intravenous fluid and for possible sepsis with penicillin and colistin. Despite these measures he died 2 hours after admission.

At autopsy the finger nail bed were cyanotic. The lung were deep red purple and diffusely edematous with only minimum aeration. The right atrium and both the right and left ventricles were dilated. The great vessel arose from the base of the heart in their usual relationship but only the left pulmonary artery arose from the main pulmonary artery (Fig. 2). The systemic and pulmonary venous return were normal. The foramen ovale was anatomically patent but was competent. The right pulmonary artery arose from the base of the left side of the aorta and passed posteriorly to the right to reach the hilum of the right lung. After giving rise to the pulmonary artery the aorta and its principal thoracic vessel were normally formed. The right ventricular wall was hypertrophied and measured 6 to 8 mm.

In the left lung the media of the small muscular arteries was hypertrophied and the intima of the elastic arteries was sclerotic. The small arteries of the right lung were similar to those seen in normal infants of this age (Fig. 3 *A* and *B*).

Case 2. A 13-day-old white male infant was hospitalized on Feb. 18, 1961 because of fast breathing and cyanosis which had been present since birth. During the first trimester of pregnancy the mother had undergone excision of a thyroglossal duct cyst. A flu-like illness had occurred shortly after the operation and lasted for 2 weeks. Delivery was uncomplicated at full term.

After an initial 3 min period of apnea respirations were rapid and associated with retraction of the thoracic cage poorly. Cyanosis cleared and respirations improved after administration of digitalis and oxygen. A heart murmur appeared 48 hours after birth.

On admission the infant was pale and exhibited respiratory distress with respiratory rate of 100 per minute and intercostal and subcostal retractions. The pre-axillary impulse was erect and the pericardial force 1 (the fifth intercostal space) at the anterior wall, 1.5 cm. The second heart sound in the pulmonary area was lower split and louder than normal. A Grade 1 (out of 4) pansystolic murmur at the lower left sternal border was followed by a short high frequency crescendo diastolic murmur at the apex there was no addition of a low pitched short mid-diastolic murmur.

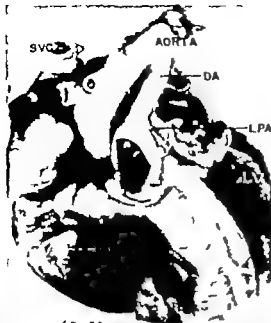


Fig 2 Case 1 1 Viewed anteriorly only the left pulmonary artery arises from the main pulmonary artery. The ductus arteriosus is patent. B Viewed posteriorly, the right pulmonary artery arises from the left a part of the aorta and then passes posterior to the aorta to reach the hilus of the right lung. SIC Superior vena cava D4 Ductus arteriosus LPI Left pulmonary artery RPI Right pulmonary artery UPI Uterine pulmonary artery PI Pulmonary veins RI Right atricle LI Left ventricle

The peripheral pulses were bounding and equal in the upper and lower extremities. No rales were heard in the lungs. The liver was soft and palpable 3 cm below the right costal margin. There was no edema of the trunk or extremities.

Poentrograms of the chest showed that the heart was dilated with enlargement of all four chambers. The pulmonary vascularity markings were more prominent than normal. The electrocardiogram indicated right ventricular hypertrophy. The T segment change was considered to be related to the administration of digitalis. Hemogram and urinalysis were normal for his age.

Since the infant would not tolerate an environment of room air cardiac catheterization was performed on the day after admission with the baby breathing 100 per cent oxygen. Morphine and atropine had been administered as premedication. Right brachial arterial oxygen saturation was 98 per cent. Right ventricular and pulmonary systolic pressures were greater than systemic arterial pressure. Left atrial pressure was elevated (35/15 mm Hg) and higher than right atrial pressure (20/10 mm Hg). Cardio Green dye curves with sampling from the right brachial artery after injection into the main pulmonary artery right ventricle and inferior vena cava showed a small right to left shunt and a large left to right shunt. Only a left to right shunt was demonstrated by injection into the left atrium. An angiogram obtained via a catheter passed through a patent foramen ovale into the left atrium showed that the right pulmonary artery arose from the ascending aorta (Fig. 4).

Surgical therapy was elected because of the critical status of the patient due to intractable cardiac failure in spite of treatment with digitalis and oxygen. An attempt at decreasing the magnitude of the left to right shunt was considered to be advisable and constriction or ligation of the ascending right pulmonary artery was planned.

Operation was performed shortly after the completion of cardiac catheterization. A left patent ductus arteriosus 7 mm in diameter was doubly ligated. The left pulmonary artery arose normally from the main pulmonary trunk. The right pulmonary artery was 4 mm in diameter and arose from the right side of the ascending aorta 1.5 cm above the aortic annulus. Because the small size of the anomalous right pulmonary artery made it unsuitable for grafting or anastomosis, it was ligated near its point of origin in order to interrupt the left to right shunt through the lungs. Cardiac action appeared to be satisfactory. The pericardium was closed loosely, and the thoracic incision repaired. After the infant arrived in the recovery room his condition deteriorated and death occurred 3 hours after operation.

Postmortem examination revealed no intra cardiac anomalies. The foramen or hole was valv competent. The main pulmonary artery gave rise to only one branch, the left pulmonary artery. The right pulmonary artery arose from the ascending aorta 1.5 cm above the annulus, followed a normal distribution and had been ligated near the aorta. The ductus arteriosus had been patent but was occluded by ligatures.

On micro-cupic examination the lungs were

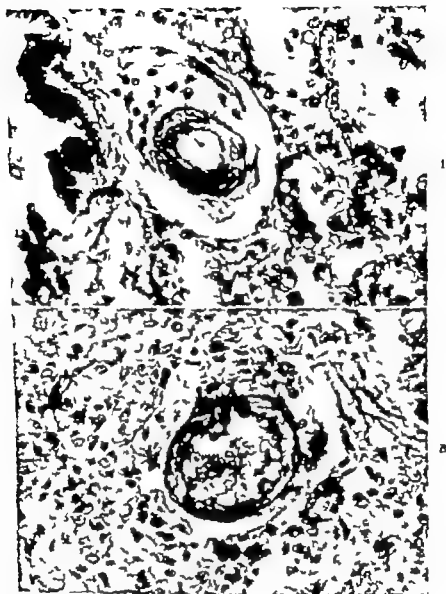


Fig 3 Case 1. In the left lung (A) the media is relatively thick, whereas in the right lung (B) the proportion of media to the entire wall is normal (Verhoeff Van Gieson $\times 160$)

found to be edematous and filled with alveolar macrocytes. Medial hypertrophy of the small muscular pulmonary arteries was noted in both lungs which were comparable to those of normal infants of the same age (Fig 3 A and B).

Case 3. This 5-month-old white male infant had had a heart murmur at birth but he did well until the age of 21 months when he developed labored and noisy respirations intermittently. Cyanosis was slowly progressive and especially marked with effort.

On physical examination the infant was cyanotic with noisy respiration, intermittent expiratory stridor and a brassy cough that was markedly

accentuated with effort. Vital signs were heart rate 160 per minute, respirations 36 per minute, blood pressure (right arm) 110/70 (left arm) 110/70 and (left leg) 118/70 mm Hg. He weighed 13 pounds and 3 ounces which placed him between the third and fourth percentiles for weight. The neck veins were abnormally distended. There was a precordial bulge with a prominent Harrison groove. Breath sounds were harsh bilaterally. The point of maximum impulse was in the sixth intercostal space midway between the mid-clavicular and the anterior axillary lines. There was a thrill over the lower left sternal border and a precordial and axillary thrust. A to-and-fro Grade 4 (out of 6) systolic



Fig. 4. Angiocardiogram with injection of contrast material into left atrium. Note the origin of the right pulmonary artery from the right side of the ascending aorta.

murmur was heard along the lower left sternal border with apical and diastolic flow murmur. A continuous murmur was heard at the base of the heart with high pitched diastolic murmur. Anjection of contrast was heard at the lower left sternal border and pericardial area was palpable 5 to 6 cm below the right costal margin.

An ECG showed a frontal QRS axis of position 130 degrees and right atrial enlargement and right ventricular hypertrophy. Chest x-ray films showed moderate to marked cardiac enlargement with slight coarctation of the pulmonary artery segment. There were increased pulmonary vascular markings and a prominent thymic shadow at the right base.

A cardiac catheter passed from the right ventricle into the aorta and then into the pulmonary artery without entering the right ventricle. The pulmonary arterial oxygen saturation was persistently greater than the systemic arterial oxygen saturation. Right and left ventricular pressures were equal. An oxygen saturation step occurred between the middle and the outflow tract of the right ventricle just beneath the aortic valve.

An esophagogram showed displacement of the esophagus and trachea to the right and upward. The baby's respiratory distress increased and digitalization was begun.

Severe cardiac failure was apparently due to a large left-to-right shunt. Because of the critical condition of the patient and lack of response to medical therapy, operation was considered to be desirable in order to decrease the magnitude of the shunt.

Operation was performed 3 days after catheterization. The pulmonary branch of the truncus was

banded. The child's respiratory difficulty increased and he died on the day after operation.

At autopsy, a truncus arteriosus arose from the base of the heart. The left pulmonary artery arose from the base of the truncus but the orifice of the right pulmonary artery was much higher, arising from a small branch which extended from the base of the innominate artery to the hilus of the right lung (Fig. 6). Bronchial arteries with an external diameter of 2 mm extended to the hilus of the right lung.

Within the heart, a defect in the interventricular septum was anterior to the crista supraventricularis. The valve of the truncus arteriosus had three cusps which were lightly thickened.

The vessel from the innominate artery to the hilus of the right lung was interpreted as a right patent ductus arteriosus. The wall was thicker and the lumen narrower than those of the left pulmonary artery or the distal portion of the right pulmonary artery.

Microscopically, the small muscular arteries of the left lung showed medial hypertrophy, whereas those on the right had a relatively thin media (Fig. 7, I and B).

Discussion

In the human embryo the definitive pulmonary arteries are formed by the ventral (proximal) rudiments of the sixth aortic arch. The distal (dorsal) components of the sixth arch connect the ventral rudiments with the dorsal aorta and constitute the ductus arteriosus on each side. Normally, the distal portion of the right sixth arch (i.e. the right ductus arteriosus) disappears and the proximal portion persists as the proximal part of the right pulmonary artery.¹ Should development be abnormal with persistence of the distal portion and disappearance of the proximal portion of the sixth right aortic arch, the right pulmonary artery would arise from the aorta through the medium of a persistent right ductus arteriosus forming a Type I origin of the right pulmonary artery from the aorta.

The embryonic truncus is separated into an aortic and pulmonary artery component by a spiral septum. Whereas absence of this septum results in a persistent truncus arteriosus, displacement of the septum results in the Type II origin of the right pulmonary artery from the aorta at the base of the heart.

The Type I defect was described by Wagenvoort and associates in a 20 day old infant. They found a right pulmonary artery arising from the aorta with the

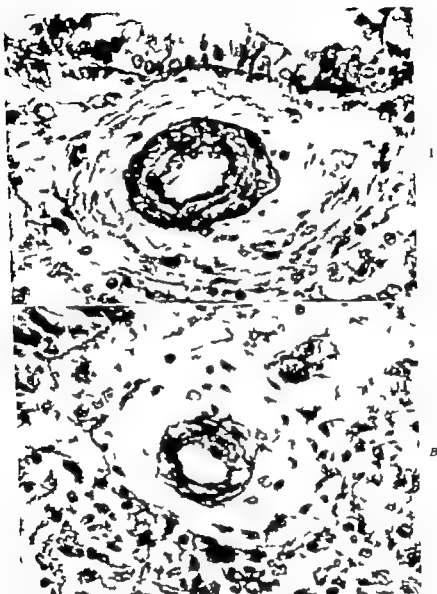


Fig 5 Case 2 The media is prominent in the small muscular arteries of the right lung (A) as well as in those of the left lung (B) (Verhoeff Van Gieson $\times 160$)

proximal portion made up of ductus-like tissue indicating the persistence of the distal portion of the arch arch and loss of the proximal portion.

In 1963 Odell and Smith⁹ reported 3 instances of patients with aortic origin of the right pulmonary artery and found mention of 11 others in the literature. The age of these patients at death was 4 months or less in 70 per cent. Pathologic data were available on 13 patients. There were 10

Type II cases with the right pulmonary artery arising from the ascending aorta and 3 Type I cases in which the pulmonary artery arose from the base of the innominate artery. Among the 8 patients in whom exact size was specified the right pulmonary artery was 3 mm or greater in 5. A majority of patients (8 of 13) had an associated patent ductus arteriosus. One patient had an aortopulmonary window. 1 had a right subclavian artery



Fig 6 Case 3 A surgically placed hand surrounds the left pulmonary artery near its origin from the truncus. The proximal right pulmonary artery is absent. The ductus extends from the innominate artery in the hilus of the right lung. DA Ductus arteriosus LPA left pulmonary artery TA Truncus arteriosus

arising from the ascending aorta and 3 had no associated anomalies.

Physiologically, an anomalous right pulmonary artery of either type functions as a left-to-right shunt much as does a patent ductus arteriosus or ventricular septal defect. This shunt plus that through a frequently associated patent ductus account for the severe heart failure seen in patients with this anomaly and may explain the short lifespan of individuals so afflicted.

The pulmonary arterial bed responds with a series of reactions to increased blood flow when the pressure is high as in the case of a ventricular septal defect. A similar vascular response is usually delayed for many years when the increased flow is under low pressures as in the case of an atrial septal defect.

Even with ventricular septal defects there is no direct correlation between pulmonary arterial structure and pulmonary blood pressure or flow.⁴ In general pulmonary hypertension with an increased blood flow is associated with medial hypertrophy of the small muscular arteries whereas pulmonary hypertension and decreased pulmonary blood flow are associated with intimal sclerosis.⁵

In the Type II defect or abnormal truncal septation the right lung is subjected to normal or low flow at systemic arterial pressure whereas the left lung is subjected to an increased flow consisting of the entire output of the right ventricle probably at an increased pressure.

Odell and Smith⁶ found no consistent pattern of pulmonary vascular structures correlating with either high pulmonary arterial flow or pressure in their review of cases with recorded pulmonary histology; however 3 cases were altered by narrowed proximal portions of the right pulmonary, thus possibly shielding the small pulmonary vessels from systemic arterial pressure. It is likely that those cases with small right pulmonary arteries were actually examples of Type I defects in which the right lung is perfused through a persistent right patent ductus arteriosus.

In our Cases 1 and 2 the malformation was Type II in each with widely patent right pulmonary arteries allowing unobstructed exposure of the right lung to systemic pressure. In Case 1 the media of the vessels of the left lung was thicker than that of the vessels of the right lung. This difference was considerably more prominent in Case 1 who lived to 7 weeks of age than in Case 2 who lived to the age of 2 weeks. This relative minor difference between the lungs in Case 2 would be expected because of the thick medial layers normally present in the first months of life. The catheterization data from Case 2 reveal the presence of pulmonary hypertension. Thus the pulmonary vascular bed of the left lung appears to have responded to increased flow and pressure by medial hypertrophy of small muscular arteries but the vascular bed of the right lung responded little or not at all to increased pressure with normal flow. In Case 3 in which the right pulmonary



Fig. 7 Case 3. A: The medial layer of the small muscular arteries of the left lung is hypertrophic. B: The left lung the medial is thin (Verboef van Geon $\times 160$).

artery arose from a ductus the pulmonary arteries of the right lung had very thin walls whereas those of the left lung showed medial hypertrophy.

Surgical treatment of a right pulmonary artery arising from the aorta should aim at interrupting the shunt and then ideally at restoring normal flow by anastomosing this vessel to the main pulmonary artery by means of a graft. Ligation of the right pulmonary artery or pneumonectomy for treatment of the origin of the right pul-

monary artery from the aorta was first suggested by Lindkvist and Maier⁶ who reported the case of a 4 month old infant with this anomaly who died from heart failure and pneumonia. Later Maier⁷ mentioned the possibility of anastomosing the anomalous right pulmonary artery to the main pulmonary trunk. In 1957 Caro, Lermundi and Lyons reported an operation upon a 23 year old man with aortic origin of the right pulmonary artery and a patent ductus arteriosus (Table I). After

Table I Surgical treatment of patients with right pulmonary artery arising from aorta

Author	Age of patient	Diagnosed preop	Operation	Results
Curo et al	23 yr	Yes	Interruption of I DA Anastomosis of RI A to MPA by means of Iva lon graft	Died from hemorrhage from lacerated intercostal vessel
Armer et al	10 mo	Yes	Interruption of I DA Anastomosis of RI A to MPA by means of Di cron graft	Survived
Wid et al	4 mo	Yes	Interruption of PDA Ligation of I PA	Dramatic relief of heart failure Died 4 weeks later of pneumonia
DuShane et al	2 mo	No	Interruption of PDA	Died
Rosenberg et al	2 yr	Yes	Ligation of I DA Ligation of RPA	Died

PDA: Patent ductus arteriosus; RI A: Right pulmonary artery; I PA: Infundibular pulmonary artery; I VA: Inferior vena cava.

closure of the ductus the right pulmonary artery was detached from the aorta and anastomosed to the main pulmonary artery by means of an Ivalon graft. Unfortunately the patient died 3 hours after operation from hemorrhage into the left chest apparently from a lacerated intercostal artery. The first successful operation for total correction of this anomaly was reported by Armer, Schumacher, and Hite,² who anastomosed a 13 mm anomalous right pulmonary artery to the main pulmonary trunk in a 10 month old patient by means of a 13 mm Dacron tube graft. A 7 mm patent ductus arteriosus was divided and sutured. Armer and associates cite Wid and Lambert³ who made a correct diagnosis of this anomaly by cardiac catheterization and angiography in a 4-month old infant. Closure of a patent ductus arteriosus and ligation of the anomalous right pulmonary artery resulted in dramatic relief of heart failure but the infant died 4 weeks later from pneumonia. DuShane and associates⁴ reported the case of a 2 month old infant with heart failure and cyanosis. A diagnosis of patent ductus was made by cardiac catheterization and angiography. A diagnosis of division and suture of a patent ductus arteriosus

and death occurred the next day. At autopsy the right pulmonary artery 1 cm in diameter was found to arise from the ascending aorta.

The value of selective angiography in the diagnosis of aortic origin of the right pulmonary artery cannot be overemphasized. Cardiac catheterization may fail to detect this anomaly and precise anatomic delineation by angiographic techniques is necessary. The poor prospect of survival makes operative therapy mandatory in the face of intractible heart failure. Closure of the commonly associated patent ductus would not be expected to control cardiac failure in most instances and ligation of the right pulmonary artery is required to interrupt the left to right shunt. Unilateral pulmonary artery ligation is compatible with survival¹ and may be all that is technically feasible if the anomalous pulmonary artery is less than 5 or 6 mm in diameter. If the anomalous pulmonary artery is greater than 5 or 6 mm in diameter it should be anastomosed to the main pulmonary trunk by means of a Dacron tube graft of suitable size. If a grafting procedure is not feasible consideration may be given to anastomosing the right pulmonary artery to the superior vena cava.

Summary

Origin of the right pulmonary artery from the aorta is a rare anomaly that may produce heart failure and death in early infancy. The lesion may result from two different developmental defects: abnormal septation of the primitive truncus or atresia of the proximal portion of the sixth right aortic arch and persistence of the distal portion as a right ductus arteriosus.

The clinical and pathologic findings in 3 infants with this defect are described.

The value of precise diagnostic studies, especially selective angiocardiography, is emphasized. Surgical treatment should be directed at interruption of the left to right shunt by ligation of the right pulmonary artery and if possible this vessel should be anastomosed to the main pulmonary trunk by means of a Dacron graft.

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Postperfusion syndrome

A review and report of 21 cases

J. A. Rezman M.D.*

Detroit, Mich.

The appearance of atypical lymphocytes in the blood of patients after open heart surgery was first described by Battle and Hewlett¹ in 1958. In 1960 Kureel and associates² reported a syndrome consisting of fever, splenomegaly, and atypical lymphocytes in the blood of patients who were operated on for cardiac disease using the cardiopulmonary bypass technique. Subsequently seven additional reports appeared describing 38 similar cases.³⁻⁹ The present study deals with 16 cases of this syndrome and the cases of 5 other patients who probably had this illness. A necropsy report is included on one patient who developed this disease and died from other causes.

Data

At Harper Hospital from July, 1959 through April, 1963, 380 major cardiovascular operations were performed utilizing cardiopulmonary bypass technique. Survival data are summarized in Table I. Fifteen of these patients were noted to develop typical postperfusion syndrome (febrile lymphocytic splenomegaly) characterized by an elevation of temperature from 100 to 103°F, with atypical lymphocytes in the peripheral blood (Table II). Splenomegaly was present in 12 patients and was never severe. Malaise was not a prominent symptom and none of the

patients complained of chest pain. In 2 patients (Cases 12 and 21) transient non-exudative pharyngitis and shotty lymphadenitis were noted on physical examination. The first of these patients also had a nonpruritic maculopapular rash which persisted for only 36 to 48 hours.

Hepatomegaly was noted in 4 patients. Hepatic function tests were abnormal in 7 of 15 patients; most commonly there were mild to moderate elevations of the serum glutamic oxaloacetic transaminase (SGOT) and/or lactic dehydrogenase (LDH). One patient (Case 7) had rather severe hepatitis during the course of the postperfusion syndrome with associated malaise and jaundice. Preoperatively the Bromsulphalein retention had been slightly elevated at 12 per cent. Postoperatively she did well until the onset of postperfusion syndrome, at which time she became jaundiced and the hepatic function tests were as follows: bilirubin 3.7 mg. per 100 ml. (direct) and 6.0 mg. per 100 ml. (total); cephalin flocculation 3+ and 4+ at 24 and 48 hours; thymol turbidity 26 units; and Bromsulphalein retention 38 per cent. Overt signs and symptoms of both hepatitis and postperfusion syndrome disappeared within 2 weeks, although mild hepatic chemical abnormalities persisted longer.

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*From the Department of Surgery, Harper Hospital, 1500 E. 14th Ave., Detroit, Mich. 48202. Reprint requests to Dr. J. A. Rezman, M.D., 1500 E. 14th Ave., Detroit, Mich. 48202.

Cardiac disease	All cases	Number of survivors	Per cent
Congenital			
Male	71	57	80.3
Female	83	66	77.6
Subtotal	156	123	78.8
Acquired			
Male	80	46	57.5
Female	144	98	68.1
Subtotal	224	144	64.3
Total	380	267	70.3

The number of lymphocytes in the blood of these patients varied from 25 to 79 per cent of the total white blood cells with atypical or Downey cells ranging

Case	Age (yr)	Sex	Blood type	Cardiac disorder	Onset days	Fever	Spleno- megaly	Hepato- megaly	HBC	Lympho- cytes(%)	Atypical lympho- cytes(%)	Hetero- phil leukia
1	15 M	O-	VSD PS	36	+	+	+	7,400	57	21	1 78	
2	15 F	O+	VSD PS	18	+	+	-	10,000	67	22	1 7	
3	9 F	O+	VSD PS	23	+	+	-	8,200	61	14	-	
4	11 F	B+	VSD	29	+	-	+	7,650	46	14	1 28	
5	3 M	A+	ASD	19	+	+	-	1,300	61	20	1 14	
6	18 M	B+	ASD PS	27	+	+	-	5,300	58	Almost all	Negative	
7	39 F	A+	MIS	13	+	+	+	7,000	69	Almost all	1 7	
8	58 M	A+	TIA	37	+	-	-	7,600	34	10	Negative	
9	28 F	A+	AS, AI	34	+	+	-	5,600	52	19	1 11?	
10	11 F	O+	TF	17	+	-	-	3,900	59	19	1 14	
11	14 F	O+	VSD	27	+	+	-	4,900	53	19	1 14	
12	28 F	B-	M	33	+	-	-	7,600	43	3	-	
13	39 M	B+	ASD	14	+	-	-	9,000	37	7	-	
14	23 M	A+	ASD	21	+	+	-	4,200	40	16	1 14	
15	37 F	A+	ASD	15	+	+	-	5,600	5	3	-	
16	13 F	AB+	VSD PS	27	+	-	-	9,600	50	Few	-	
17	37 F	A+	ASD	33	+	-	-	8,100	60	Few	-	
18	8 M	O+	ASD	14	+	-	-	7,400	5	None	-	
19	21 F	O-	ASD	15	+	+	+	7,300	38	None	-	
20	31 F	O+	M	18	+	+	-	6,800	46	None	-	
21	23 M	O+	None	31	+	Splenec- tomy	-	23,300	9	60	Negative	

[illegible]

from 3 to 60 per cent. Total white blood cell counts were normal in 19 patients with leukocytosis of 10 700 and 23 300 per cubic millimeter in the other 2 patients. Absolute neutropenia was noted in many patients with a marked shift to the left which included the appearance of myelocytes and promyelocytes. Eosinophilia was found in 2 patients (Cases 10 and 21); it ranged from 6 to 11 per cent.

Hemoglobin, hematocrit and total red blood cell counts showed corresponding values and were either normal or mildly decreased. In those patients in whom they were low, there had been a slow decline from the immediate postoperative period with stabilization and no decrease during the acute phase of the postperfusion syndrome. Reticulocyte counts in 6 of these patients revealed a range from normal (less than 1 per cent) to a maximum of 6.4 per cent. Normoblasts were noted in 2 patients. Platelet counts in 3 patients showed normal or slightly increased values. Heterophil agglutination titers determined in 12 of the 15 patients were nondiagnostic. In Case 9 the titer was 1:132 but differential absorptions were not positive (guinea pig kidney 1:28 and beef red cells 1:14).

Multiple blood cultures were performed on all of these patients and were negative for bacteria and fungi.

In 5 other patients the classic triad of signs and symptoms was markedly present (Cases 16 through 20). All had intermittent fever and 2 had splenomegaly. Atypical lymphocytes were present in small numbers or were not reported from smears of peripheral blood. Although studies were not available for review. The delayed onset of signs and symptoms with a normal white blood cell count and lymphocytosis suggests that these patients belong in this disease group.

Two of the 21 patients had not undergone cardiopulmonary bypass. The first (Case 8) had been subjected only to left ventricular bypass without artificial oxygenation during operation for a thoracic aortic aneurysm. The second patient (Case 21) had had a ruptured spleen removed after an automobile accident and no cardiopulmonary bypass had been used. It is interesting that this splenic patient had

the highest white blood cell count, the greatest number of lymphocytes and the greatest number of Downey cells. The SGO was 66 during the course of the illness and heterophil titers were negative on three occasions.

Cardiac disease in the first 20 patients consisted of 15 cases of congenital defects, 3 cases of rheumatic valvulitis and the 1 case of thoracic aortic aneurysm. The patients with congenital heart disease made up 75.0 per cent of the cases of postperfusion syndrome and the patients with acquired heart disease comprised only 25.0 per cent.

The onset of signs and symptoms varied from 14 to 37 days postoperatively and persisted from 1 to 4 weeks. In general the fever subsided first and the splenomegaly and the atypical lymphocytes in the peripheral blood remained the longest although usually not more than a month after the patient had been discharged from the hospital.

However one patient (Case 1) developed congestive heart failure 16 days postoperatively; it was partially controlled with digitalis and diuretics. Thirty-six days after operation he developed typical postperfusion syndrome. Five days later he died from intractable heart failure. Necropsy revealed fibrinous pleuritis and pericarditis and further examination of the heart showed that the Teflon graft had torn loose from the site of repair of the ventricular septal defect and that a 4 cm opening was present. Mediastinal lymphadenopathy was present. The liver weighed 2 000 grams and had a prominent lobular pattern. The spleen weighed 540 grams with bulky red soft parenchyma that had a decreased follicular pattern. Microscopically the heart showed fibrosis and granulation tissue near the site of septal repair. The liver revealed chronic passive congestion with nucleated red blood cells in the sinusoids. An inflammatory infiltrate was noted in the portal areas and consisted chiefly of large and small mononuclear cells. The spleen exhibited small lymphoid follicles some of which had germinal centers. The red pulp was congested and the trabeculae were partially obscured by large and small mononuclear cells. The vessels and capsule

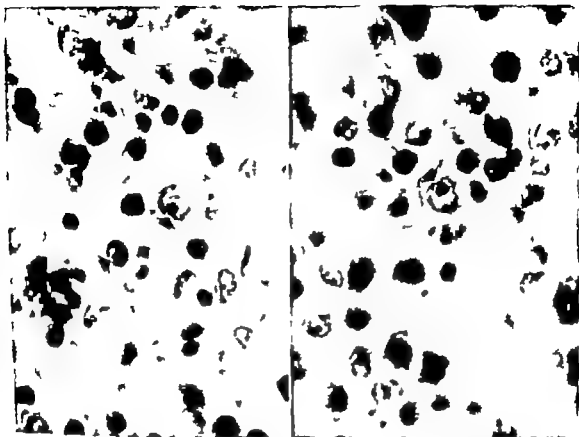


Fig 1 Sections of the spleen from a patient with postperfusion syndrome reveal several large basophilic mononuclear cells within the sinusoid which contain phloxine positive inclusion like masses that the reader (a) resembles viral inclusion bodies. Similar inclusions were noted in the cells of the lymph nodes (Phloxine hematoxylin $\times 1710$)

were normal. Phloxine hematoxylin stain revealed phloxine positive slightly irregular structures within the nuclei of many of these cells. These masses were distinct from the chromatin and nucleoli and resembled inclusion bodies (Fig 1). The lymph nodes contained similar cells which had these inclusions within the nuclei. The bone marrow was hyperplastic with an apparent increase in the erythroid series.

Discussion

A review of the findings in the 82 reported cases of postperfusion syndrome (Table III) reveals a wide variety of normal as well as abnormal diagnostic laboratory examinations. Test of hepatic function revealed elevated levels of SGOT, SGPT and LDH, most of which were mild and transient.^{12,13} Also, high values were

noted for thymol turbidity,¹⁴ cephalin flocculation,¹⁵ alkaline phosphatase and Bromsulphalein retention. Similar abnormalities were noted in this study, and the development of jaundice in one patient in the present series has not been reported previously. These data suggest that there is a hepatic component to the postperfusion syndrome although the chemical abnormalities might be a result of operative cardiac injury in some cases. The findings in the patient who had only splenectomy and a SGOT of 66 unit, as well as the more severely deranged values in other cases noted in this study, tend to support the former explanation.

Hematologic abnormalities other than those previously described are apparently not common or consistent. Ierliche and Glenn noted eosinophilia in their 3 cases, and 2 patients in this study also had high

Item	Series number										Total	Per cent
	1	2	3	4	5	6	7	8	9	10		
Number of cases	1		6	3	11	14	1	9	14†	21	82	100
Fever	†		4	3	11	14	1	7	14	21	75	91.4
Splenomegaly		1	6	3	7	12	—	9	7	12	57	69.5
Hepatomegaly			3	3	—	9	—	1	3	4	23	28.1
Normal WBC			5	2	9	11	1	7	—	19	84	65.6
Lymphocytosis			6	3	11	11	1	—	—	26	48	38.5
Atypical lymphocyte	1	2	0	3	11	0	1	9	14	18	71	86.6
Heterophil positive		1			1	1	—	2	3	—	8	9.8
Lymphadenopathy				3	—	1	—	7	1	2	14	17.1
Rash				—	—	—	—	4	2	1	7	8.5
Edema				—	—	—	—	1	1	2	4	4.9
Onset (in days)			19-48	20-30	8-42	71-49	50	21-55	13-32	14-37		
Sex												
Male			5	2	—	6	—	3	8	8	32	39.6
Female			1	1	—	8	1	6	6	13	36	43.9
Age												
<20 yr	1	—	1	1	—	7	1	9	6	10	38	46.3
>20 yr			5	—	—	7	—	—	8	11	31	37.8
Cardiac disease†												
CHD	1		3	3	—	11	—	9	10	15	54	65.9
AHD			3	—	—	1	1	—	3	5	13	15.9
Other			—	—	—	—	—	—	1	1	2	2.4

Numbers of case of measles were 10 in 1970, 15 in 1971, 16 in 1972, 17 in 1973, 18 in 1974, 19 in 1975, 20 in 1976, 21 in 1977, 22 in 1978, 23 in 1979, 24 in 1980, 25 in 1981, 26 in 1982, 27 in 1983, 28 in 1984, 29 in 1985, 30 in 1986, 31 in 1987, 32 in 1988, 33 in 1989, 34 in 1990, 35 in 1991, 36 in 1992, 37 in 1993, 38 in 1994, 39 in 1995, 40 in 1996, 41 in 1997, 42 in 1998, 43 in 1999, 44 in 2000, 45 in 2001, 46 in 2002, 47 in 2003, 48 in 2004, 49 in 2005, 50 in 2006, 51 in 2007, 52 in 2008, 53 in 2009, 54 in 2010, 55 in 2011, 56 in 2012, 57 in 2013, 58 in 2014, 59 in 2015, 60 in 2016, 61 in 2017, 62 in 2018, 63 in 2019, 64 in 2020, 65 in 2021, 66 in 2022, 67 in 2023, 68 in 2024, 69 in 2025, 70 in 2026, 71 in 2027, 72 in 2028, 73 in 2029, 74 in 2030, 75 in 2031, 76 in 2032, 77 in 2033, 78 in 2034, 79 in 2035, 80 in 2036, 81 in 2037, 82 in 2038, 83 in 2039, 84 in 2040, 85 in 2041, 86 in 2042, 87 in 2043, 88 in 2044, 89 in 2045, 90 in 2046, 91 in 2047, 92 in 2048, 93 in 2049, 94 in 2050, 95 in 2051, 96 in 2052, 97 in 2053, 98 in 2054, 99 in 2055, 100 in 2056, 101 in 2057, 102 in 2058, 103 in 2059, 104 in 2060, 105 in 2061, 106 in 2062, 107 in 2063, 108 in 2064, 109 in 2065, 110 in 2066, 111 in 2067, 112 in 2068, 113 in 2069, 114 in 2070, 115 in 2071, 116 in 2072, 117 in 2073, 118 in 2074, 119 in 2075, 120 in 2076, 121 in 2077, 122 in 2078, 123 in 2079, 124 in 2080, 125 in 2081, 126 in 2082, 127 in 2083, 128 in 2084, 129 in 2085, 130 in 2086, 131 in 2087, 132 in 2088, 133 in 2089, 134 in 2090, 135 in 2091, 136 in 2092, 137 in 2093, 138 in 2094, 139 in 2095, 140 in 2096, 141 in 2097, 142 in 2098, 143 in 2099, 144 in 2100, 145 in 2101, 146 in 2102, 147 in 2103, 148 in 2104, 149 in 2105, 150 in 2106, 151 in 2107, 152 in 2108, 153 in 2109, 154 in 2110, 155 in 2111, 156 in 2112, 157 in 2113, 158 in 2114, 159 in 2115, 160 in 2116, 161 in 2117, 162 in 2118, 163 in 2119, 164 in 2120, 165 in 2121, 166 in 2122, 167 in 2123, 168 in 2124, 169 in 2125, 170 in 2126, 171 in 2127, 172 in 2128, 173 in 2129, 174 in 2130, 175 in 2131, 176 in 2132, 177 in 2133, 178 in 2134, 179 in 2135, 180 in 2136, 181 in 2137, 182 in 2138, 183 in 2139, 184 in 2140, 185 in 2141, 186 in 2142, 187 in 2143, 188 in 2144, 189 in 2145, 190 in 2146, 191 in 2147, 192 in 2148, 193 in 2149, 194 in 2150, 195 in 2151, 196 in 2152, 197 in 2153, 198 in 2154, 199 in 2155, 200 in 2156, 201 in 2157, 202 in 2158, 203 in 2159, 204 in 2160, 205 in 2161, 206 in 2162, 207 in 2163, 208 in 2164, 209 in 2165, 210 in 2166, 211 in 2167, 212 in 2168, 213 in 2169, 214 in 2170, 215 in 2171, 216 in 2172, 217 in 2173, 218 in 2174, 219 in 2175, 220 in 2176, 221 in 2177, 222 in 2178, 223 in 2179, 224 in 2180, 225 in 2181, 226 in 2182, 227 in 2183, 228 in 2184, 229 in 2185, 230 in 2186, 231 in 2187, 232 in 2188, 233 in 2189, 234 in 2190, 235 in 2191, 236 in 2192, 237 in 2193, 238 in 2194, 239 in 2195, 240 in 2196, 241 in 2197, 242 in 2198, 243 in 2199, 244 in 2200, 245 in 2201, 246 in 2202, 247 in 2203, 248 in 2204, 249 in 2205, 250 in 2206, 251 in 2207, 252 in 2208, 253 in 2209, 254 in 2210, 255 in 2211, 256 in 2212, 257 in 2213, 258 in 2214, 259 in 2215, 260 in 2216, 261 in 2217, 262 in 2218, 263 in 2219, 264 in 2220, 265 in 2221, 266 in 2222, 267 in 2223, 268 in 2224, 269 in 2225, 270 in 2226, 271 in 2227, 272 in 2228, 273 in 2229, 274 in 2230, 275 in 2231, 276 in 2232, 277 in 2233, 278 in 2234, 279 in 2235, 280 in 2236, 281 in 2237, 282 in 2238, 283 in 2239, 284 in 2240, 285 in 2241, 286 in 2242, 287 in 2243, 288 in 2244, 289 in 2245, 290 in 2246, 291 in 2247, 292 in 2248, 293 in 2249, 294 in 2250, 295 in 2251, 296 in 2252, 297 in 2253, 298 in 2254, 299 in 2255, 300 in 2256, 301 in 2257, 302 in 2258, 303 in 2259, 304 in 2260, 305 in 2261, 306 in 2262, 307 in 2263, 308 in 2264, 309 in 2265, 310 in 2266, 311 in 2267, 312 in 2268, 313 in 2269, 314 in 2270, 315 in 2271, 316 in 2272, 317 in 2273, 318 in 2274, 319 in 2275, 320 in 2276, 321 in 2277, 322 in 2278, 323 in 2279, 324 in 2280, 325 in 2281, 326 in 2282, 327 in 2283, 328 in 2284, 329 in 2285, 330 in 2286, 331 in 2287, 332 in 2288, 333 in 2289, 334 in 2290, 335 in 2291, 336 in 2292, 337 in 2293, 338 in 2294, 339 in 2295, 340 in 2296, 341 in 2297, 342 in 2298, 343 in 2299, 344 in 2300, 345 in 2301, 346 in 2302, 347 in 2303, 348 in 2304, 349 in 2305, 350 in 2306, 351 in 2307, 352 in 2308, 353 in 2309, 354 in 2310, 355 in 2311, 356 in 2312, 357 in 2313, 358 in 2314, 359 in 2315, 360 in 2316, 361 in 2317, 362 in 2318, 363 in 2319, 364 in 2320, 365 in 2321, 366 in 2322, 367 in 2323, 368 in 2324, 369 in 2325, 370 in 2326, 371 in 2327, 372 in 2328, 373 in 2329, 374 in 2330, 375 in 2331, 376 in 2332, 377 in 2333, 378 in 2334, 379 in 2335, 380 in 2336, 381 in 2337, 382 in 2338, 383 in 2339, 384 in 2340, 385 in 2341, 386 in 2342, 387 in 2343, 388 in 2344, 389 in 2345, 390 in 2346, 391 in 2347, 392 in 2348, 393 in

7 per cent. Wheeler and associates⁴ reported similar findings and direct antiglobulin tests on 2 patients were negative. Holmsted and associates⁶ did not consider anemia to be a feature of the postperfusion syndrome. On the other hand Profsky¹² noted 7 cases of hemolytic anemia in the postoperative period in patients who had undergone aortic valve surgery, 4 of whom also developed febrile lymphocytic sple nomegaly. Direct antiglobulin tests in these patients were positive. Although the association of hemolytic anemia in these 4 patients tends to suggest the contrary situation anemia per se does not appear to be a component part of the post perfusion syndrome in view of the findings in the 32 cases reviewed here.

Serologic tests included heterophil agglutination titers which were reported to be positive in 8 cases. Toxoplasma antibody tests have been uniformly negative.¹¹ Antistreptolysin O tests when

performed¹⁴ have been nondiagnostic and an antihuman antibody test performed in one case was negative.⁷ Widal agglutination, lupus erythematosus and direct antiglobulin tests performed in a few cases were negative.²

The etiology of the postperfusion syndrome remains unknown. The pump oxygenator has been eliminated as a cause since this illness developed in 2 patients in this study who had not been operated upon using the cardiopulmonary bypass technique and also in 2 cases reported by Bastin and associates⁹ as well as in the 23 cases noted by Bergstrom and Dahlstrom¹⁵ (This latter group of patients was operated on for tuberculosis).

There is good evidence that the syndrome is not due to bacterial or fungous septicemia since hundreds of blood cultures in the 82 patients reported on have not demonstrated a single positive result. The likelihood that the illness is infectious in nature is strongly suggested by other data. Although many authors have noted a sporadic occurrence, 12 of the 23 cases of postperfusion syndrome presented here occurred between September and January and there was also a very high incidence in 1959 despite a similar number of oper-

ations each year. Wheeler and associates,¹ Holswade and associates⁸ and Smith⁶ found similar, apparently seasonal distributions in their cases. A viral etiology is suggested by the inclusion like particles noted within the cells of the spleen and lymph nodes in the necropsied case reported here.

The postperfusion syndrome most closely resembles infectious mononucleosis (Table IV)^{16,17} with fever, splenomegaly and atypical lymphocytes. Other less common signs and symptoms noted in infectious mononucleosis are also seen in postperfusion syndrome and these include pharyngitis, lymphadenopathy, skin rash, normal white blood cell count, hepatic chemical abnormalities, variable incubation time and a generally benign course. The postperfusion syndrome appears to develop more commonly in patients with congenital heart disease than in those with acquired heart disease although this may be a manifestation of the youth of the former.

The clinical and hematologic findings noted in most of these cases are not diagnostic of infectious mononucleosis and perhaps the most compelling reason to consider postperfusion syndrome as a

Table IV. Comparison of postperfusion syndrome to other symptomatic disease conditions

Item	Infectious mononucleosis	Postperfusion syndrome	Acute infectious lymphocytosis	Serum sickness
Age	Less than 30 usually	Less than 30 usually	Children	All age
Sex	M 2 F	?		
Onset	Delayed	Delayed	Delayed	Delayed
Fever	+	+	+	+
Lymph node enlargement	+	±	±	+
Splenomegaly	+	+	-	-
Heterophily	±	±	-	-
Pharyngitis	+	-	±	±
Rash	±	±	±	+
Leukocytosis				
Lymphocytes	Moderate to normal	Usually normal	Mixed	Moderate
Neutropenia	+	+	+	-
Atypical lymphocytes	+	+	+	+ Early
Heterophil	+	±	-	-
Etiology	?	?	-	-
Course	Usually benign	Benign	Benign	Foregoing protein usually benign
Signs prolonged	+	+	-	±

+ = Less than 50% prevalence; ± = Variable prevalence; - = Usually absent

form of infectious mononucleosis is the positive heterophil agglutination titer reported in some of these cases. However even a suggestive heterophil titer is not proof of infectious mononucleosis since relatively high titers have been noted in other circumstances.¹⁷ I am at present investigating the possibility of the formation of atypical or incomplete heterophil antibodies in some of these patients as the cause of negative agglutination titers. Also blood from 2 patients is being cultured by Dr Helene Schneider of Baptist Memorial Hospital Memphis Tennessee who reports that she has developed a technique that renders a specific cytopathic effect in tissue culture with sera from patients with infectious mononucleosis.¹⁸ Other possible etiologies that have been suggested are a leukocyte graft versus host reaction^{9,11} and the activation of a latent endogenous virus by the stress of the operation. Dr Wolf Zuelzer (of Children's Hospital Detroit Michigan) thinks that this latent endogenous virus might behave in a manner similar to that theorized for herpes simplex virus.

Differentiation of the postperfusion syndrome from other postoperative complications usually is not difficult. Postperfusion cardiotomy syndrome (postconstrictoromy syndrome) has a delayed onset and may consist of paroxysmal attacks of fever, malaise, chest pain and pleural and/or pericardial effusions.² The symptoms are usually controlled with aspirin or steroids which are of uncertain benefit in postperfusion syndrome.¹⁹ Usually, no splenomegaly is present and there is often a neutrophilic leukocytosis.

The postperfusion pulmonary congestion syndrome occurs in the immediate postoperative period and is characterized by fever, dyspnea and cyanosis.^{1,4} The peripheral blood picture is usually not compatible with postperfusion syndrome and this cyanotic dyspneic state appears to be a serious complication which often results in the death of the patient.

Septicemia or endocarditis may mimic in many ways the postperfusion syndrome but the clinical course and the blood culture studies have in my experience pointed out the true etiology in those cases which came to necropsy at a later date. Of the

4 such cases 3 patients developed proved *Candida septicemia* and the fourth patient had *Micrococcus albus* cultured from the blood, valve mortem and from the diseased aortic valve at necropsy. In all cases the septicemia developed weeks after surgery in that period during which most patients have developed postperfusion syndrome and this fact suggests that blood cultures and other diagnostic tests should not be abandoned too quickly.

Summary

Twenty one cases of postperfusion syndrome are described. The illness consists of fever, splenomegaly and atypical lymphocytes in the peripheral blood after cardiopulmonary bypass and occasionally after other operative procedures in which large quantities of blood are transfused. Infrequently the heterophil agglutination titer will be positive as noted in cases reviewed from the literature. The illness which is benign in its course closely resembles infectious mononucleosis although other agents may be responsible. Differentiation from other postoperative complications and possible etiology and pathogenesis are discussed.

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Fundamentals of clinical cardiology

Apex cardiography

E. Grey Dimond, M.D.*

Asaria Duenas, M.D.

Alberto Benchemol, M.D.

La Jolla, Calif.

For the past several years we have studied the possible usefulness of apex cardiography. We have described our results in a series of papers.¹⁻⁴ In recent literature other workers have described their experiences.⁵⁻⁸ Hurtmann⁹ in particular stimulated our initial interest.

Technique

We have now recorded several thousand apex cardiograms and although this figure is irrelevant the number is over ten thousand. From this experience we can make these generalizations:

1. An apex cardiogram by our definition refers to a recording made at the point of maximal impulse with the patient in a left lateral position and in mid expiration.

2. If a right heart cardiogram is desired the patient is supine in mid expiration and the recording is made from the area of maximal pulsation which is identified by eye and hand.

3. Whether apex cardiogram or right heart cardiogram the pulsation is first visualized on an oscilloscope and the pickup piece is shifted slightly until a tracing demonstrating a clear O point (opening of the mitral or tricuspid valve) and a clear initial systolic lift (isometric contraction)

is seen on the oscilloscope. If these two physiologic events can be clearly discerned then the vibration is considered to be adequate for analysis and recording is made. Note this variable. Although the point of maximal impulse identifies the location for application of the pickup, still further adjustments of location are necessary by viewing the tracing on the oscilloscope until these two basic landmarks can be seen. The pickup piece is applied quite firmly and is held in place by hand. Respiration is suspended.

The following additional variables must be considered:

A. *Size of pickup* The diameter of the funnel which comes into contact with the skin may vary from 2 to 5 cm. depending upon the extensiveness of the precordial movement. A sharply localized thrust may be analyzed with a small pickup; a larger area of movement may require a pickup of larger diameter. The timing of events is not varied by changing pickup; however the contour, especially the latter half of systole, can be altered by this variable.

B. *The frequency range of the apex cardiogram* We have attempted to confine our studies to the frequency range which is undoubtedly below the hearing range, specifically below 25 cycles per second.

From the University of California Department of Medicine, Scripps Clinic and Research Foundation, La Jolla, Calif.
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Address: Scripps Clinic and Research Foundation, 426 Prospect St., La Jolla, Calif.

We have accomplished this by filtering out frequency variations above this range. There is no uniform agreement upon this subject however and the term apex cardiogram is used by various workers to include vibrations of a higher spectrum.

C Characteristics of the sensing device. We have used the Sanborn crystal microphone No. 374 and the Schwarzer transducer Z101/37 and have found a quantitatively similar apex cardiogram. However we have not performed the necessary analysis of each of these microphones and we do not know their response characteristics. Later in this paper we cite the correspondence from Eddleman who has not found the frequency response of the Sanborn microphone to be linear (*infra vide*).

The obvious possibility that the apex cardiogram as described here is a synthesis not only of true cardiac events but also of nonspecific rotation of the heart and of resonance of the thoracic cage all compounded by some digital dexterity on the part of the operator makes this technique suspect. If the method is admitted to be a crude attempt to quantitate physiologic events and if it is accepted that more refined instrumentation will come along then there still is sufficient reason at the present to attract the clinician. There is also sufficient factual physiologic information to make this method of interest to the investigator.

The results with apex cardiography in recent years can be summarized as follows.

1 The apex cardiogram faithfully records the onset of ventricular contraction and when used in conjunction with the carotid trace and phonocardiogram offers an indirect means of determining isometric contraction ejection time isometric relaxation ventricular filling time and the interval from the onset of atrial systole to the initiation of isometric contraction.^{1,2,4}

2 The apex cardiogram is a useful reference tracing and provides a time record of the onset of left ventricular filling and the rate of left ventricular filling and therefore analysis of this phase of the apex cardiogram can be useful in the discrimination of mitral regurgitation from mitral stenosis.^{3,7,8} The 2 QS interval can be determined in the absence of an opening

snap by measuring the interval from the second heart sound to the O point.^{1,4}

3 The apex cardiogram records the precordial vibration associated with atrial contraction and the recorded tracing is useful in quantitating the amplitude of this vibration. The clinical usefulness of this fact needs further study however. Our own studies have indicated a considerable relationship between the presence of an abnormal left ventricle and a large atrial wave vibration. This relationship can be further defined as follows.

4 A large atrial component is present in those conditions in which a thickened compensated left ventricle is present—*aortic stenosis subaortic obstructive disease hypertensive cardiovascular disease any nonspecific myocardialopathy*.^{1,2,10,11}

5 A large atrial component is present in ischemic heart disease in the presence of an apparently compensated left ventricle of normal size. There seems to be a direct relationship between the extent of the ischemia and the amplitude of the atrial component. Exercise will exaggerate the amplitude of the atrial vibration whereas nitroglycerin will result within minutes in a marked decrease or even disappearance of the atrial vibration.^{1,2,7,10,12} Aging alone is not associated with this enlarged atrial component.^{13,14}

6 The large atrial vibration has some quantitative relationship to the level of the left ventricular end-diastolic pressure.^{4,15}

7 In a patient with ischemic heart disease and with a large atrial vibration and an elevated left ventricular end-diastolic pressure who clinically is *not* decompensated acute digitalization will not alter the large a wave nor the elevated end-diastolic left ventricular pressure. The a wave does not decrease and the left ventricular end-diastolic pressure does not decrease yet immediately thereafter in the same patient sublingual nitroglycerin will decrease both the end-diastolic left ventricular pressure and the amplitude of the atrial wave. This observation has suggested to us that during angina pectoris there is an elevated left ventricular end-diastolic pressure and that this elevated pressure does not represent one usual concept of left heart failure but that instead we must consider an alternative to

heart failure. A loss of left ventricular compliance during ischemia has been suggested.^{2,7,12,36}

E In patients with ischemic heart disease in whom an elevated left ventricular end diastolic pressure and a large atrial component in the apex cardiogram are recorded not only nitroglycerin but also venous tourniquets will reduce to normal or near normal these two parameters. Furthermore a tight abdominal binder (Kerr-Lugen belt) will cause this same alteration toward normal. These observations suggest that at least one of the effects of nitroglycerin is to decrease venous return.^{3,10,22,32}

F In some individuals with ischemic heart disease smoking results in an increase of atrial vibration and venous tourniquets prevent this alteration. This observation suggests that one of the actions of smoking is to increase venous return.²⁷

In summary an increased atrial component to the apex cardiogram seems to be a constant sign of an abnormally functioning left ventricle. It is not diagnostic and cannot be used to separate conditions of hypertrophy, ischemia or failure. However from our present experience the measurement of the amplitude of the atrial vibration expressed as a ratio of the total vibration at rest and after exercise seems to be a valuable screening procedure for identifying the presence of left ventricular disease. The difference in response of the atrial component to nitroglycerin and to digitalis may offer a means of separating primary ischemic disease from cardiac failure. Physical and pharmacologic agents may be appraised by suitable measurements.

F The apex cardiogram in chronic left ventricular heart failure records prominent atrial waves and left ventricular filling waves (IV and III heart sounds). These alterations in the atrial wave can be returned toward normal by digitalis.⁴⁰⁻⁴²

G In the presence of idiopathic hypertrophic subaortic stenosis the apex cardiogram frequently presents an abnormal systolic contour with an initial sharp rise, a fall off and a second systolic dome—similar to the percussion and tidal waves of the arterial pulse. The apex cardiogram in idiopathic hypertrophic subaortic ste-

nosis therefore frequently presents as a useful almost diagnostic tracing with a prominent atrial wave, a sharp quick systolic rise, a fall off and a rounded domed wave in later systole.^{1,12,32} The site of the point of maximal impulse may be medial and superior in this condition and it is this location to which we are referring.

G In myocardial infarction particularly if recent but also in patients experiencing angina pectoris at the moment of the recording a double systolic wave is recorded—a late systolic bulge, a sustained systolic wave.^{1,7,14,33,34,35} Such a wave form in ischemic heart disease may represent a true myocardial aneurysm or may be but a temporary paradoxical movement due to the ischemia.^{33,34,35}

G A retracting impulse may be recorded in constrictive pericarditis and in association with pleuropelvic adhesions.^{1,4}

The principal comments so far in this paper have related to the tracing obtained from the point of maximal impulse, thus the term apex cardiography. The same technique can be used to obtain a record of the movement of any area of the precordium (In fact identical equipment is used for recording the venous trace and the carotid trace in the neck.) We have restricted our analysis to the precordium and in addition to the left ventricular vibration we have recorded in patients with right heart disease adequate tracings from the xiphisternal junction and from the fifth intercostal space in the immediate parasternal line. Prominent right heart waves are quite characteristic of pulmonary stenosis and pulmonary hypertension. The right heart cardiogram in rheumatic panvalvular disease has a close correlation to physiologic events. The possible usefulness of such recordings in congenital heart disease has been defined.^{11,12,32,44-45}

Related techniques

Although we have discussed only apex cardiography other workers are accumulating similar and additional information using other techniques for recording precordial vibrations. These methods and their chief proponents are (1) kinesiocardiology (Eddleman-Harrison), (2) vibrocardiography (Arewa), (3) impulse cardiog-

raphy (Mourvet) and (4) precordial accelerography (Rosa Lusada).

A brief resume of the relationships and differences between these methods is given in Table I. The left hand column lists the methods and the accepted abbreviation of the terms. One method vibrocardiography records a broad sound spec-

trum the other four record selectively the low frequency audible range.

We have recently corresponded with the individual workers and several current comments are significant. Lusada states that studies of the Altec Lansing microphone demonstrate a sharp drop in its response below 30 cycles per second and

Table I. Technical differences between methods

Method	Frequency range (cycles per sec.)	Pick up used	Characteristic transducer	Point of reference or position
Kinetocardiography (KCG)	D.C.-70	Metal bellows and piezo-electric transducer (Statham P5A)	Displacement	ECG precordial lead (V ₁ to V ₆)
Apex cardiography (ACG)	0.1-20	Schwarzer transducer or Sanborn crystal microphone J-4 (with filter)	Displacement	Maximal apical impulse
Impulse cardiography	1-10	Photoconductive cell (O.R.P. 90 Mollard)	Displacement	Cardiac impulse in selected sites (pre left parasternal and right parasternal areas)
Vibrocardiography (VBCG)	30-300	Altec Lansing capacitor microphone	Velocity and displacement	Fourth intercostal space 1 cm from left sternal border
Precordial accelerography (PACT)	5-75	Electromagnetic transducer	Acceleration	Fourth intercostal space 1.3 cm to the left of left sternal border

Table II. Range of published studies

Disease	Method	References
1 Ischemic heart disease	KCG ACG VBCG PACT	3 6 7 33-36 38 39 41-4 55 58 60 63
2 Mitral valve disease	KCG ACG Impulse cardiogram	1 3 5 1 35 48
3 Aortic valve disease	KCG ACG	3 8 13 29 3 5 64 65
4 Hypertrophic subaortic stenosis	ACG	8 9 30
5 Idiopathic cardiac myopathy	ACG Impulse cardiogram	8 29 31 48
6 Ventricular hypertrophy	KCG ACG Impulse cardiogram PACT	1 3 7 9 11 13 15 20 1 5 6 8 3 3 4 44 46 49 55 58 64 65
7 Congenital heart disease	KCG ACG Impulse cardiogram	11 13 3 46-48
8 Reference tracing	ACG	1 2 4 5 15
9 Medication effect of		
a Exerx	KCG ACG VBCG PACT	3 6 15 33 35 39 43 44 60 63
b Nitrates	KCG ACG	2 3 6 7 33 35 39 41
c Digitalis	KCG	40 41
d Smoking	ACG	7

that low frequency tracings with it are questionable. Furthermore correspondence from Eddleman states that he has found the kinetocardiography system to be fairly linear from D C to 20 cycles with a resonance at 80 cycles per second. He further found that the apex card diagram has a marked roll off in amplitude response below one cycle per second with a marked phase shift both in the low frequency as well as in the upper ranges.⁴⁰

Current correspondence from Mounsey⁴¹ states that he has compared his impulse cardiography to the kinetocardiography metal bellows pick up using the same subject. Almost identical curves were obtained in relation to timing and direction of the wave. Differences between the kinetocardiography method and (the impulse method) are due to two main points: (1) The amplification of our tracings both for the healthy subject and in heart disease is constant. Thus although the deflection of our tracings in health is small their amplitude can then be compared with that seen in the presence of ventricular hypertrophy where the patient shows clinically a large sustained outward lift. (2) The force applied to the chest wall by the instrument pressing upon it is probably greater in the case of the kinetocardiographic metal bellows than with our impulse cardiograph. We have measured the force exerted by the light springs in our instrument and found it to be between 100 and 200 grammes over the range of displacement measured. Due to the stiffness of the metal bellows of kinetocardiography I imagine that especially with large movements of the chest wall the force exerted by the kinetocardiographic probe on the chest wall must be of greater order. Since by exerting force in the intercostal space one can presumably actually displace the heart backwards slightly this is another cause of minor differences between our two displacement records.

Agnew⁴² advised us that he has changed his nomenclature from the letter system to the numbering system with the anticipation that this would be more practical and would eliminate some of the confusion arising from association with ballistocardiography (see Fig. 1).

Table II provides an index to the pub-

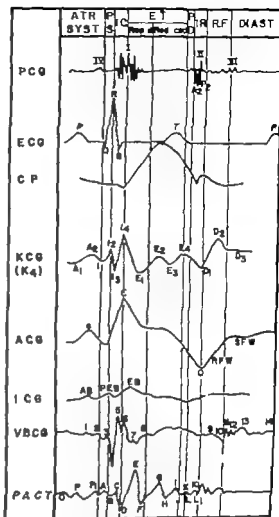


Fig. 1 Correlation of the records obtained with the various techniques. See text.

lished studies with these various approaches.

Fig. 1 attempts to correlate the records obtained with these various techniques. The apparent dissimilarity is misleading; instead, note that all tracings document major vibrations synchronous with cardiac events.

Summary

For the past several years we have studied the possible clinical usefulness of recording the low frequency precordial vibrations put in motion by the cardiac cycle. We have confined our analysis to the technique of apex cardiography. Our approach has been that of clinical empiricism.

specifically, we have prestated the clinical variable using standard disease patterns and then analyzed the apex cardiographic response to this variable. Subsequently, we altered pharmacologic and physical variables and again noted the apex cardiographic response.

Simultaneously and in some instances earlier, other investigators have also studied precordial vibrations using the same or different methods. The consensus seems to indicate that there is clinically useful information to be gained by analysis of this low frequency spectrum. It is important to appreciate this fact inasmuch as the diversity of instruments, nomenclature and method may alarm and dissuade others from gaining experience in this field.

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Appraisal and reappraisal of cardiac therapy

Edited by Arthur C DeGraff and Alan F Lyon

Antianginal drugs

Part VI Beta-adrenergic blocking agents

Solomon Fisk MD*

Bronx N Y

In order to explain the biologic differences between various sympathetic amines it has been hypothesized that there are two types of adrenergic or sympathetic tissue receptors. These are called α and β adrenergic receptors. These new designations replace the confusing old terms of excitatory and inhibitory sympathetic actions. It should be emphasized that this is only a working hypothesis. α Adrenergic receptors are responsible for vasoconstriction and for contraction of the uterus, nictitating membranes, pupillary muscles, splenic capsule, and palomotor apparatus; they also mediate relaxation of the intestine. β Adrenergic receptors cause vasodilatation, relaxation of the myometrium and bronchi, and augmentation of the rate and force of contraction of the heart. Epinephrine mediates the action of both receptors. Norepinephrine and isoproterenol are virtually pure α and β adrenergic receptor stimulants respectively. Antagonists to α adrenergic receptor action or α blockers include phentolamine (Regitine), piperocin hydrochloride (Benodrine HCl), and phenox benzamine hydrochloride (Dibenzyline). β Blockers have been developed only recently. They are being studied primarily because of their potential usefulness in cardiovascular therapy. They appear to act by competitive inhibition of their respective catecholamines. The first β

blocker dichloroisoproterenol (DCI) bore structural similarity to isoproterenol. It was discarded because it had too much sympathetic activity of its own. Subsequently, pronethalol and propranolol and several others which are in various stages of investigation were introduced. Despite minor differences, these compounds behave pharmacologically in similar fashion and will be discussed as a group with major emphasis on their cardiovascular effects.

Cardiovascular effects. Compounds suspected of having β adrenergic blocking ability are screened by their ability to block the cardiovascular effects of exogenous isoproterenol. Compounds that do this have been considered to block the effects of endogenous β adrenergic stimulation as well.

The exact role of the myocardial β adrenergic receptors and of the endogenous amines that presumably mediate their myocardial effects is unknown. In resting normal men β blockers have no effect. In hypertensive subjects at rest a modest lowering of cardiac output, left ventricular work, heart rate, and brachial arterial pressure occurs. In both groups during or after exercise the drugs reduce pulse blood pressure, cardiac output, and left ventricular work, and increase heart size, stroke volume, and systolic ejection time. There is a slight decrease in the velocity of contrac-

Diuretic treatment of primary lymphedema

Primary lymphedema is an uncommon but by no means rare cause of peripheral edema. It occurs three times more commonly in women than in men and a familiar form of acral edema is obtained in some 20 per cent of patients. The etiology and pathology of this condition remained obscure until the introduction of lymphangiography demonstrated a basic defect in the lymphatic channels. The site of this defect lies in the main subcutaneous lymph trunks and may be one of three types. Aplasia of the lymph trunks is present in about 10 per cent of cases when no formed lymph trunks can be demonstrated. This is commonest as occurred with severe and progressive lymphedema which becomes clinically manifest in infancy. More commonly in some 75 per cent of affected subjects there is hypoplasia of the lymph trunks with abnormalities in both the size and the number of the lymphatics. Although also a congenital maldevelopment this defect may not become apparent until adolescence or early adult life and in general has a relatively benign course. The lymphatic defect in the other 15 per cent of cases is one of atresia or dilated and tortuous lymph trunk with marked incompetence of these channels as evidenced by backward flow and lateral spread of dye on lymphangiography. This type of defect is commonly evident in infants as severe and progressive rapidly.

The functional result of these defects is a failure in the normal removal of particles of large molecular size from the interstitial space by the lymphatics. In particular the small quantities of plasma proteins which enter the interstitial space are not removed but accumulate. Their osmotic activity results in an increase in subcutaneous fluid and clinical edema. Studies of edema fluid have confirmed a high content of proteins and investigations using ¹²⁵I albumin have defective removal of the labeled protein from lymphoedematous limbs. This latter observation is in contrast to the increased removal of subcutaneous injected ¹²⁵I albumin in subjects with edema due to heart failure, hypoproteinaemia or venous obstruction.

Clinically the typical patient with primary lymphedema is an adolescent girl or young woman with spontaneous edema of one or both legs. Initially there may be only slight painless pitting edema of the ankle most evident in the evening and commonly worse in hot weather or before menstruation. The initial complaint is largely cosmetic but as the disease progresses the limbs become more swollen, heavy and burdensome. Secondary fibrosis

in the subcutaneous tissue develops with or without recurrent attacks of cellulitis. Lifting no longer is possible and the swelling becomes more constant. In general edema is greatest and it progresses more rapid in patients with lymphatic aplasia or atresia of lymphatics.

Diagnosis depends on exclusion of other systemic causes of edema, analysis of the protein content of the edema fluid (> 1.5 Gm. per cent) and lymph angiography.

Treatment of this condition in the past has been far from satisfactory. In advanced cases considerable benefit may be obtained from surgical treatment but the need for this is a reminder of our inability to control the condition in its earlier stages before gross unsightliness and disability develop. Conservative management of lymphedema which includes elevation of the limb and support by bandaging is regularly unsatisfactory. Although such therapy may be acceptable to patients with extremely severe and disabling edema few subjects with mild swelling are prepared to follow this regimen. It is however in mild cases that treatment is possibly more necessary for it has been suggested that failure to control the early accumulation of protein rich interstitial fluid leads to recurrent infection and progressive fibrosis with irreversible changes in the subcutaneous tissues.

In view of the success of modern diuretic therapy in the management of patients with cardiac renal and hypoproteinaemic edema it is not surprising that such therapy has been advocated for subjects with lymphedema. On theoretical grounds it might be expected that diuretic therapy would be of only limited value in a condition in which edema appears to result primarily from the local accumulation of osmotically active interstitial protein and not from the inappropriate renal retention of sodium and water as in cardiac renal and hypoproteinaemic edema. Early reports on the use of diuretics in this condition claimed that they were effective. However few patients were studied and in the main these had advanced disease. Furthermore no clear distinction was made between patients with primary lymphedema and those with venous insufficiency.

A more critical assessment of the place of diuretic therapy in this disorder has recently been carried out. In a carefully controlled study 27 patients in whom primary lymphedema was diagnosed were included in a double blind crossover trial. The design of the trial was such that the results obtained

were not affected by spontaneous changes in the lymphoedema due to menstruation climatic conditions or arduous dietary habits. The response to therapy was evaluated both on the patient symptoms and subjective assessment and on measurements of body weight and limb circumference and volume. The drug employed was chlorothalidate in a dose of 500 mg twice daily for 5 days in 7. Each patient was studied for at least 28 weeks 14 weeks on therapy and 14 weeks on placebo with the order randomised.

The study showed great differences in the response to therapy varying from nil to considerable in individual cases. Subjective improvement was claimed by 11 of the 25 patients who completed the trial but corroborative objective evidence was lacking in 4. Amongst the 14 patients who improved there was considerable symptomatic and/or objective improvement in 3 moderate improvement in 2 and only marginal improvement in 7. An additional 3 patients with objective evidence of considerable reduction in edema did not adhere to any symptomatic improvement. Over all worth while improvement was deemed to have been achieved in 10 of 11 patients and was considerable in 8 of the 10. In no case could it be considered that the lymphoedema was completely eliminated.

Follow up studies on the 6 patients showed the improvement to be maintained for periods up to 8 months. A 3 month follow up of 13 patients who failed to improve during the trial period demonstrated only slight improvement in 3 patients during this more prolonged period on diuretic therapy.

A retrospective analysis of the results of this trial failed to reveal any clear-cut criteria by which to select patients likely to respond to diuretic therapy. Thus the presence or degree of improvement could not be clearly connected with the degree or duration of the condition although there was some suggestion that more severely affected subjects responded more often and more markedly. No correlation could be demonstrated between the response to therapy and a history of premenstrual aggravation of the edema or premenstrual tension.

It is concluded that diuretic therapy could be of considerable benefit in certain patients with lymphoedema. The dosage schedule employed was safe and devoid of side effects. No clear selection possible of patients likely to respond to treatment and for this reason objects should be given a 3

month trial period. Patients failing to respond to this program are unlikely to benefit from more prolonged treatment.

H R Cattell MD MRCP MRCPA
Senior Lecturer in Medicine
G H Taylor MS FRCS
Professor of Surgery
St Bartholomew's Hospital
London England

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Endocardial pacing

In 1952 Zill described a technique of artificial pacing of the heart which employs electrodes placed on the heart wall directly along the conduction system at 25 to 150 V. It is an indirect method of pacing through the conduction system.

patient was used in a case of a patient with a long life expectancy with Stokes-Adams attacks due to a stroke. An alternative method of temporary pacing by the transvenous route was not desirable because of the risk of thrombosis.

in 1958 using a unipolar electrode passed via a peripheral vein into the right ventricle temporary pacing was then possible with low voltages and without discomfort to the patient.

Techniques suitable for long term pacing of the heart were developed independently by Chardack and colleagues¹ and Limqvist and Senning² in 1960 which consisted of direct stimulation of the heart by electrodes implanted at thoracotomy and attached to buried abdominal pacemakers. Reports of experience of long term pacing by epicardial electrodes with or without implanted pacemakers have now been published by many authors. The principal disadvantage of epicardial pacing is the necessity for a thoracotomy in a group of patients largely in their sixth and seventh decades which often results in complications serious enough to consider alternative methods of pacing. However, Vowchuk and colleagues³ and Hirsch and colleagues⁴ have placed the epicardial electrode through an upper abdominal and lower lumbar splitting incision and this technique has considerably lowered the morbidity of epicardial pacing.⁵⁻¹²

Many patients who were considered to be too old or ill for thoracotomy or who refused operation were treated by endocardial pacing using unipolar or bipolar electrode catheters introduced via the jugular venous system or occasionally the cephalic vein. It was thought that this method of pacing for long term treatment would prove to be unsatisfactory because the electrode position would be unstable and there might be complications such as septicaemia embolism and myocardial perforation.¹³⁻¹⁵ Reports have now appeared however confirming the advantages of endocardial pacing for the long term treatment of heart block.¹⁶⁻²⁰ The initial position of the electrode tip in the right atrium (particularly with a unipolar catheter) is critical for maintenance of pacing and placement is greatly facilitated by using a high-definition image system for preferably with a field of vision or more. Bipolar electrode catheter pacing is technically easier and the position in the right atrium is not so critical but these electrodes have not proved to be entirely satisfactory because of fractures of the wire.²¹⁻²³ When the unipolar endocardial electrode is made the positive pole less power is required to pace the heart than with the bipolar electrode and this is an important consideration when the electrode is attached to an implanted pacemaker and lowers the possible risk of producing ventricular fibrillation but suffers from the disadvantage that the subcutaneous positive pole may occasionally cause troublesome local stimulation of skeletal muscle. With bipolar electrode pacing the current is completed through the blood in the right ventricle and this results in the deposition of fibrin and the formation of thrombus by the negatively charged blood elements depositing on the positive pole which may result in a progressive rise in the threshold for pacing and the occurrence of pulmonary emboli. With unipolar endocardial pacing the formation of thrombus

has never been a problem and anticoagulant therapy is unnecessary.¹⁶⁻²⁰ Perforation of the heart by the C50 No 5 endocardial electrode has occasionally occurred usually at the time of insertion of the electrode catheter or as a late complication when attached to an external pacemaker and the larger and more rigid bipolar catheters may be worse in this respect. Fortunately perforation of the heart by an endocardial electrode has not so far resulted in serious sequelae and it is usually possible to continue pacing after the endocardial electrode has been repositioned.²⁴

When the endocardial electrode is externalized to the neck or anterior chest wall and attached to an external pacemaker the chief complications are the relative ease with which a patient can accidentally pull the electrode out of position and the risk of septicaemia from the small risk of infection which occurs around the electrode site of exit in the skin.²⁵ Septicaemia is particularly liable to occur if the electrode has to be repositioned in the presence of local infection or in the presence of rheumatism or congenital heart disease (a contraindication to endocardial pacing if an external pacemaker is used). If septicaemia does occur cure with antibiotics is only likely to be achieved if the endocardial electrode is removed.¹⁶⁻²⁰ Nevertheless despite these hazards successful endocardial pacing with an external pacemaker has been reported in patients for as long as 3 years.¹⁶⁻²⁰

A logical development in the technique of endocardial pacing was implantation of the pacemaker thereby reducing the risks of septicaemia and accidental displacement of the electrode from a satisfactory pacing position in the right atrium and avoiding the risk of fractured endocardial catheters in patients with rheumatic or congenital heart disease. A few months after installation of an endocardial system using the unipolar C50 No 5 electrode with an implanted pacemaker in the axilla some electrodes fractured resulting in a intermittent pacing a complication not associated with unipolar endocardial pacing and an external pacemaker.²⁶⁻²⁸ The stream of current occurred in the electrode at the point at which the catheter was inserted into the jugular venous system and was due to angulation of the electrode catheter in the neck during movements of the shoulder which moved the implanted pacemaker in the axilla. It was probably better to implant the pacemaker unit in the anterior chest wall thereby avoiding the mechanical stress on the C50 No 5 electrode catheter which occurs with movement of the shoulder when the unit is implanted in the axilla. Implantation of the unit in the anterior chest wall is usually possible in most women but not always in thin men because of the size and shape of the pacemaker unit. With the thin patient a coiled stainless steel link between the pacemaker unit implanted in the axilla and the C50 No 5 electrode catheter in the anterior chest wall may avoid stress fractures.²⁹ An alternative is to use the external pacemaker with the endocardial electrode catheter having no moving contact surface on the anterior chest wall.³⁰ Recently more flexible electrode catheters have been developed³¹⁻³³ for use with implanted pacemakers but they are more difficult to introduce into the right atrium via the

jugular venous system and the results of their long term use have not yet been reported.

Abrams⁸ has adapted an induction system of pacing to an endocardial electrode and this is proving to be satisfactory. The secondary coil is attached to a short length of a CSO No. 5 electrode catheter and buried in the anterior chest wall. Because of the location of the coil and attached electrode catheter very little movement occurs in the electrode on movement of the shoulder joint and stress fractures have not occurred during 15 months of experience in 16 patients. This method of endocardial pacing combines the ease of servicing of the pacemaker unit which is possible with an external pacemaker and the low rate of arrhythmias and stability of the endocardial electrode expected with an implanted pacemaker.

Endocardial pacing has proved to be a valuable addition to the short term and long term management of heart block. The use of a unipolar endocardial electrode requires considerable experience for satisfactory placement and until experience has accumulated poor results may be obtained. For this reason the bipolar system may prove to be preferable when only the occasional patient is to be treated since its placement is less critical.

The main problem of maintenance of satisfactory pacing with implanted pacemakers is the production of a reliable pacemaker unit. Recently Duck⁷ reviewed pacemaker failure and it appeared that most commercially available units have a high incidence of component or battery failure. Unless tremendous attention to detail and very careful checking of components such as transistors and batteries are carried out at every stage of manufacture of pacemaker units a proportion of them will continue to fail prematurely.

I. M. Harris M.B.B.S. M.R.C.P.
Cardiac Department
St George's Hospital
London S.W.1 England

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Atrioventricular and intraventricular conduction defects after nonpenetrating trauma

Atrioventricular and intraventricular conduction defects are not frequently reported as following nonpenetrating bodily trauma. We were able to find 21 reported cases of the former¹ and 14 of the latter condition.²⁻¹¹ Atrioventricular conduction disturbances consisted of various degrees of AV block from prolonged P-R¹² to complete heart block.¹³⁻¹⁷ They occurred either as a transient¹⁸⁻²⁰ or as a permanent phenomenon.²¹⁻²³ Intraventricular conduction defects also occurred both transiently and permanently.²⁴⁻²⁶

A review of the literature shows that nearly two thirds of the cases of AV block were described from 1912 to 1938; the remainder were described from 1939 to 1964 despite the enormous increase in number of traumatically injured persons encountered in these last 25 years. Moreover, the exact role of trauma is difficult to ascertain in many published cases. Therefore it is the purpose of the present paper to review criteria for establishing causal relationship of trauma to atrioventricular and intraventricular conduction defects.

Heart conditions before trauma. To determine up the full role of trauma it would be ideal if heart studies could be obtained before and after injury. Unfortunately this is often impossible and the past history of the patient must be determined by careful detective questioning. (It is odd that in 10 reported cases of traumatic sinoatrial and intraventricular block no electrocardiogram had been recorded before trauma.) Now for as certain as it is well known that complete congenital heart block was treated with other important cardiac malformations not only may be completely asymptomatic but also may not be diagnosed accurately during a medical visit. This condition is therefore very difficult to exclude in a young patient who acquires heart trauma and has a very known history of heart block in the years following trauma. Such were the outstanding features of 7 reported cases of traumatic complete heart block.²⁷ The age of onset for acquired complete heart block occurred before the occurrence of trauma in three not easily ruled out when the patient is middle aged or old. Sention and associates²⁸ reported that in some adult patients in whom heart block was discovered on routine examinations no symptoms had been present previously. The presence of sinus bradycardia or AV conduction defect or of complete or bifascicular bundle branch block in a certain percentage of a large, healthy population²⁹ furthermore point out the importance of electrocardiographic examination prior to trauma.

It has been stated that a diseased heart is more susceptible to traumatic injury than is a normal heart.³⁰ In a human case trauma in the preexisting factor of aortic dissection. A pathologic cardiac process was evident in 6 reported cases in

which trauma was with the greatest probability the trigger mechanism of AV block.³¹⁻³⁶ The presence of previous diseases capable of producing myocardial impairment was revealed by the post history in 9 other cases.³⁷⁻⁴⁵ Gore³⁷ reports with this a latent subclinical heart disease may be a source of error in attributing post-traumatic symptoms and signs to trauma itself. Unfortunately no criteria exist to prevent diagnosis of the error in such cases. This is particularly true for conduction defects. Cases are reported of patients in whom death occurred within a few hours after repeated Adams-Stokes attack and in whom the clinical and electrocardiographic findings had been normal just before the terminal illness despite the complete destruction of the conduction system found at autopsy.⁴⁶

Traumatic pathology of the conduction system. Although a disturbance in the autonomic nervous mechanism of the heart has been claimed to be responsible for the transient appearance of an AV block after trauma,⁴⁷ hemorrhages and lacerations at the conduction system level are the more commonly postulated cardiac lesions in cases of permanent atrioventricular and intraventricular block.⁴⁸ Nevertheless the following clinical and experimental data stress that only with great difficulty can a healthy conduction system be injured sufficiently to produce permanent atrioventricular and intraventricular conduction defects. For instance 10 reported cases of closed traumatic rupture of the interventricular septum have been reviewed by one of us⁴⁹ only 1 case out of 20 in which clinical or electrocardiographic records were available was complicated by complete heart block. Furthermore a AV induction was absent also when the rupture was extensive located high up in the interventricular septum and surrounded by extensive myocardial hemorrhage. In 1 of 12 patients in whom an electrocardiogram was recorded showed atrioventricular conduction defects: 4 had right bundle branch block and 1 had left bundle branch block in them rupture was located in the middle and upper portion of the septum. Surgical repair of cardiac septal defects report at another situation in which injury occurred in the immediate proximity of the conduction system in such an event heart block appears only in about 10 per cent of the cases and is transient in 70 per cent of them. Sometimes only right bundle branch block is evident despite the finding of large areas of hemorrhage and infarction of the common trunk and both bundle branches on histologic examination.⁵⁰

Experimentally in dogs, rats and with limited data in 1937 Schibye⁵¹ found that intraventricular heart block appeared in only 17 of 76 calls in which he had been told upon the heart that he observed no permanent disturbance of AV

conduction. In dogs struck on the chest by heavy hammer blows changes in atrioventricular and intraventricular conduction tended to be transient unless the insults were repeated. Pathologic evidence of myocardial injury (consisting mainly of subendocardial or subepicardial hemorrhages) was strikingly small and in some cases edema of the myocardial fiber of the conduction system was postulated.¹⁰ It has also been demonstrated in dogs that the left upper part of the endocardial surface of the interventricular septum may be deeply cut and extensively lacerated without producing a permanent left bundle branch block.¹¹

Conclusions. Basic criteria to be used in assessing traumatic etiology of heart block can be summarized in this youthful age of the patient: absence of pre-existing heart diseases or conduction defects; great magnitude of the injuring force; electrocardiographic findings suggestive of myocardial involvement (abnormalities of both the QRS and the T wave); associated traumatic heart lesions (e.g., interventricular septal defect or rupture of the aortic valve); absence of a long latent period between the time of injury and the discovery of block.

Three reported cases of traumatic A-V block, 10 cases of right bundle branch block, and 2 cases of left bundle branch block satisfy most or all of these criteria and can therefore be considered to be of proved traumatic etiology. The incidence of each type of conduction defect within this group might not be causal but related to the anatomic architecture of the conduction system, which accounts for easier stretching and interruption of the right bundle than of the left or of the common bundle. In other reported cases¹²⁻¹⁵ of traumatic etiology, most in our opinion, be considered to be either possible or probable but not proved. Two cases cannot be taken into consideration since the clinical findings are not sufficient to assess the presence of heart block.

A critical attitude toward traumatic disturbances of intraventricular and atrioventricular conduction defects seems therefore to be necessary, although we acknowledge that there are also important exceptions to any general rule. For instance, the large magnitude of the injuring force that is set up as a blunt criterion may not be indispensable since a relatively small force applied under ideal circumstances can injure a particular organ. This may apply as well to the conduction system.

Liberto Dolara M D
Lucio P M D
Electrocardiographic Service
Hospital of S M Ann
Florence Italy

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On the role of hydralazine in renal hemodynamics and secretion of renin

It has been known in the past by various investigators that hydralazine is a vasodilator drug increasing renal blood flow. Except for pyrogen,¹ normally no other agent has been found to have such a specific effect upon the renal circulation.

Recently it was observed in the rat² that the intravenous administration of hydralazine decreases the concentration of sodium and increases the electrical resistance in the renal medulla without any significant alteration in either parameter in the cortex.³ In view of the fact that after hydralazine the glomerular filtration rate remains unchanged, these medullary changes were attributed to an augmentation of medullary blood flow.⁴ Thus a simple way was made on the basis that changes in the medullary concentration of sodium are inversely related to alterations in the medullary blood flow (countercurrent diffusion exchange mechanism).⁵

Most recently it has been reported that after alterations in the renal hemodynamics by renal artery stenosis, mainly or by constriction of the thoracic aorta in the dog,⁶ a marked increase in venous plasma renin activity is observed after intra-

venous injection of hydralazine by using a rat (Sprague). Most interesting in the observations that the cause of unilateral renal artery stenosis after hydralazine increase in renin activity is not only in the renal venous plasma of the affected side.⁷ Another important finding is that renin activity is not altered after injection of pentolinum, reserpine or the beta-adrenergic blocking agent propranolol.⁸ This suggests that the action of hydralazine in increasing the secretion of renin is unique and is probably not mediated by a neurogenic or humoral mechanism.

Taking into consideration our own work and the observations of others,⁹⁻¹² the following points with regard to the role of hydralazine on renal hemodynamics and the secretion of renin is made. It is well known that the zona glomerulosa secreting renin is located in the peripheral portions of the cortex and that granular cells are prominent toward the juxtaglomerular junction and absent in the medulla.¹³ Usually after hydralazine, an increase in total renal blood flow occurs. Our data imply indirectly the possibility that this increase

in flow is more prominent in the medulla than in the cortex. Perhaps because of autoregulation which operates mainly in the cortex¹¹ the cortex copes with the situation and thus cortical blood flow remains unchanged. Under abnormal conditions however particularly when renal artery stenosis is present the autoregulating mechanism of the cortex may be defective because of the presumably ensuing reduction in perfusion pressure and the renal vasoconstrictor effect of hydralazine. Hence a relative increase in medullary blood flow after hydralazine could mean a redistribution of blood from cortex to medulla and a relative cortical anemia which in turn might result in underdistention of the stretch receptors in the afferent arterioles. This would account for more granularity of the cells and an increased secretion of renin.

In summary it is suggested that under the circumstances of reduced intrarenal perfusion pressure or diminished renal blood flow as a consequence of renal artery stenosis or coarctation of the thoracic aorta an increased medullary blood flow after the administration of hydralazine could further alter the intrarenal hemodynamics and lead to an increase in the secretion and activity of renin.

*Ignazio J. Voudoukis M.D.
Division of Hypertension
Henry Ford Hospital
Detroit Mich 48202*

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Book reviews

ELECTROLYTES AND CARDIOVASCULAR DISORDERS
Vol. II CLINICAL APPROACH Edited by Egon Bajusz
In print at Montreal Baltimore 1966 The
Williams & Williams Co. \$12.00 Price \$16.

Volume II of this series contains short papers by many authors writing on other aspects of electrolyte metabolism in cardiovascular diseases. This volume is divided into two parts. Part A is concerned with pathologic and physiologic problems and Part B is concerned with prevention and therapy. Part A presents discussions of primary myocardial disease, potassium depletion, potassium and the electrocardiogram, the shift of the ST segment and arterial hypertension. In Part B the discussions are of potassium treatment, the use of electrolytes in cardiopathies and in the treatment of myocardial infarction, potassium and the AV node and the use of Mg and K in cardiac therapy. Introduction is neglected to a great extent. On the whole this volume is good one and the two volumes together provide a fine source of information on electrolytes and cardiovascular diseases. Both volumes should prove to be very useful to internists, cardiologists and physiologists and will provide the undergraduate students with interesting and useful information. Experts in this field will find the ideas to be proposed and will not agree with all thought expressed but will find interesting problems that need investigation.

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INTRAVASCULAR CATHETERIZATION Edited by Henry
A. Zimmerman MD 85 St Vincent Charity
Hospital Cleveland Ohio ed 2 Springfield Ill
1966 Charles C Thomas 1297 pages Price \$39.50

This book, edited by Dr. Zimmerman with 26 contributors is a very good edition. The first edition met with considerable success. This edition was expanded and is quite comprehensive. The beginner as well as the experienced radiologist will find the presentation not only useful but it will read and the text clearly illustrated. There are chapters on the unique method of analysis of curves, applications of method in diagnosis, interpretation of data, congenital and acquired heart disease, pulmonary circulation, cerebral blood flow, coronary circulation, and other. The techniques of x-ray angiography and cine x-ray angiography are discussed very well. The biographies are good and there are good subject indexes. This book runs over a thousand pages in length is encyclopedic in nature. It is highly recommended as a reference source. It is a book worth owning on the subject of cardiac catheterization.

The Hearst Edited by J. Willis Hurst M.D. and H. Bruce Logan M.D. New York 1966 Black 1000 Division McGraw Hill Book Company 1255 pages Price \$25

Hurst and Logue have edited a good book on cardiology, with 66 contributors representing various fields. The book is similar in design to Cecil and Loeb's textbook of medicine. Like Cecil and Loeb's, this book tends to be brief but at the same time includes a thorough coverage of major problems of cardiology, including the peripheral vessels. However, the section on the peripheral vessels is not only inadequately presented but also is disproportionately small in comparison to the surgical aspect. The illustrations are clear, the book is profusely illustrated and the bibliography appended to each section are good. With this very fine textbook of cardiology, Hurst and Logue have made an excellent contribution to the field of medicine. Students, general practitioners, internists and cardiologists should find this book to be very useful and will want to own a copy.

Books received

CAROL FOR THE AIR PD By Benjamin B. Allen with
Former Agent N. Y. 1966 (Doubleday) & Co
100 372 pages (1966 \$4.95)

LIBRARY STATE OF HYPERBARIc MEDICINE Publication No. 1298 prepared by the Committee on Hyperbaric Oxygenation with support of the National Institutes of Health Public Health Service and the Office of the Surgeon General, Department of the Army, Washington D. C. 1966 National Academy of Sciences National Research Council 178 pages Price \$6.

MATHEMATICS IN MEDICINE AND THE LIFE SCIENCES
By George R. Stibitz. Chicago, 1966. Year Book
Medical Publisher, Inc. 321 pages. Price \$12.50.

MODERN TREATMENT Vol 3 No 2 March 1966
 1. Treatment of Neurovascular Disorders by
 Frank M Howard M.D. Presently practicing in
 New York City. 1966. 110 pp. \$10.00
 Modern Treatment of Neurovascular Disorders
 1966. 110 pp. \$10.00

Charles C Wolferth

Dr Charles C Wolferth died at the hospital of the University of Pennsylvania on Dec 26 1965 three hours after he had correctly recognized the initial symptoms of aortic dissection. In the seventy eighth year of his vigorous life he was fully active in practice. Within the year he had shared the platform with Dr Francis C Wood in conducting the weekly seminars of the Department of Medicine. Two weeks before his death he had lectured in his capacity as Eminent Professor to the third year class on angina pectoris. He was the moderator of the weekly conference of the Cardiac Section and his daily private rounds continued to be a prime educational experience for students and house officers.

Dr Wolferth was born in 1887 at Wolferth Station New Jersey. He worked on his father's farm in his youth and subsequently attended Princeton University. He was on the varsity football and swimming teams and was elected to Phi Beta Kappa en route to his bachelor's degree in 1908. After transferring to the University of Pennsylvania for medical training he continued to play varsity football and to attain scholastic honors. He was president of his class when he received the degree of M.D. in 1912. His internship was served at the Hospital of the University of Pennsylvania (1912-1914) followed by a residency in Pathology (1914-1916). He was then appointed as the first Chief Medical Resident at the University Hospital (1916-1917). After this he entered the military services and served in France as Chief of the Medical Service of Base Hospital No 31 stationed at Contrexville in Lorraine. At the termination of hostilities and prior to his return to the United States



Charles C Wolferth 1887-1965

Major Wolferth attended several of the newly formed hospital cardiac clinics in London and he was assigned for a time to the British Military Heart Hospital under the professional direction of Sir Thomas Lewis. Dr Wolferth was one of several American graduates of that institution who returned to his university to organize a cardiac subspecialty group within the department of medicine. At the University of Pennsylvania the Cardiac Section was developed by Dr Wolferth to investigate observe and report that which would contribute to medical knowledge in the cardiovascular field. He was the Director of the Cardiac Section and also

Director of its research arm the Edward B. Robinette Foundation for Cardiovascular Research until his official academic retirement in 1952. In actuality, he never did retire from any of his professional interests and activities.

Dr. Wolferth's name appeared on 140 publications over a period of 47 years. Many of his close professional associates collaborated with him on these papers, including Drs. T. M. McMullan, Alfred Stengel, T. G. Miller, T. Fitz Hugh, J. Edeiken, S. Bellet, E. Rose, F. D. Murphy, J. J. Sayen, W. F. Sheldon, A. M. Sellers, A. G. Hills, H. F. Zinner, C. W. Crumpton, and M. M. Laveze. The subject matter ranged broadly across the cardiovascular field: quinidine and digitalis arrhythmias, experimental myocardial ischemia, hypoxia, heart muscle lesions, and the electrocardiogram; angina and gall bladder disease; and angina relief by thyroid depression are examples. Many of these papers continue to be widely quoted, but he will be best remembered for his outstanding contributions in auscultation, electrocardiography, and adrenalectomy for hypertension.

Fourteen references are directly concerned with the mechanisms responsible for heart sounds. Much of this work was undertaken in close collaboration with Dr. Alexander Margolies. They utilized sound recording techniques which were advanced in design for the time combined with roentgenology, arteriography, and venous pulse recording and electrocardiography in the study of the factors influencing the intensity of the first heart sound and of the mechanisms of gallop rhythm, opening snap sound, and systolic clicks. Their observations contributed greatly to the present understanding of cardiac auscultatory phenomena.

Throughout his professional life, Dr. Wolferth was greatly interested in the theory and practice of electrocardiography. A paper entitled "The Electrocardiographic Diagnosis of Coronary Occlusion by the Use of Chest Lead," by C. C. Wolferth and F. C. Wood, was published in the *American Journal of Medical Sciences* in January, 1932. Although chest lead had been employed in related instances for decades, especially in the study of arrhythmias,

this was the first demonstration of the tremendous advantage of precordial electrode placement in the diagnosis of myocardial infarction. It led to the utilization of chest leads as a standard clinical procedure within a very short time. Another paper entitled "The Mechanism of Production of Short P-R Intervals and Prolonged QRS Complexes in Patients with Presumably Undamaged Hearts: Hypothesis of an Accessory Pathway of Auriculoventricular Conduction (Bundle of Kent)," also by C. C. Wolferth and F. C. Wood, offered the concept of accelerated A-V conduction in the explanation for this curious disorder. This memorable publication proposing an alternative to the atypical conduction block concept appeared in the *AMERICAN HEART JOURNAL* in 1933. Ten years later, Wood, Wolferth, and Geckler demonstrated an accessory atrioventricular muscular connection in the heart of a subject who had had in life the short P-R interval syndrome.

In 1949, Green's report of subtotal adrenalectomy in a hypertensive diabetic patient led Dr. Wolferth to initiate a major program. Adrenalectomy, with and without sympathectomy, was performed in 184 severely hypertensive patients. Dr. H. A. Zintel performed most of the surgical procedures. Dr. W. A. Jeffers, Dr. A. C. Hills, and Dr. F. D. W. Lukens collaborated with Dr. Wolferth in the intensive study of these patients, which continues under the direction of Dr. A. M. Sellers. Adrenalectomy proved to be an effective therapy for severe hypertension at a time when alternative therapy was poor. None of the patients who were operated upon subsequently developed congestive failure, an observation of significance in relating adrenal function to congestive failure. The 84 survivors continue to be a source of great investigative interest. Dr. Wolferth was the author or co-author of 27 of the 81 publications that have derived from this clinical and experimental study of by far the largest group of patients subjected to adrenalectomy.

In 1922, Dr. Wolferth married Mary Beatrice Comber, who preceded him. A son, Dr. C. C. Wolferth, Jr., is Clinical Associate Professor of Surgery at Hahnemann Medical College. Two daughters of

that marriage also survive. In 1950 Dr Wolferth married Dr Mary Laveez, Chief Cardiologist of the Chestnut Hill Hospital in Philadelphia.

Dr Wolferth will long be remembered for his outstanding contributions to medical science and his remarkable skill as a physician and teacher. A less tangible but

equally important memorial is in the hearts and minds of the many physicians who profited mightily from his wisdom and guidance.

*Cedric F. Kay, MD
Hospital of the University
of Pennsylvania
Philadelphia, Pa*

Editorial

Observations on the vascular anatomy of the pituitary gland and its importance in pituitary function

Peter V Daniel D V D Sc FRCP

London England

Marjorie M L Prichard M A D Phil*

Oxford England

It has been known for a considerable time that the anterior lobe of the pituitary gland (hypophysis cerebri) produces a number of specific hormones but the means by which the production and release of these hormones are controlled was for long obscure. There was no convincing evidence that the cells of the anterior lobe were innervated and yet there were strong indications that the release of most of these hormones was under hypothalamic control.^{1,2} In recent years it has become increasingly apparent that the pathway through which this hypothalamic control is exercised must be that formed by the hypothalamo hypophyseal nerve tract and the system of hypophyseal portal vessels. Some knowledge of the detailed anatomy of this unique neurovascular complex is essential therefore if one is to understand the means by which the central nervous system exerts its profound influence on the functions of the anterior pituitary. Our own studies of the pituitary have been

largely concerned with its circulation and thus with the vascular component of the hypothalamo hypophyseal pathway. In the following account we review briefly some of the findings which we have obtained in both anatomic and functional studies which seem to be of special interest because of their physiologic or pathologic implications. The observations were made on the glands of human subjects, monkeys, sheep, goats and rats. More detailed accounts with illustrations will be found in our other papers.

The pituitary gland is made up of three readily identifiable parts: the anterior lobe which is composed of epithelial cells of characteristic secreting type; the posterior lobe which consists of nervous tissue; and the stalk which links these two lobes with the hypothalamic region of the brain. The stalk consists of a tract of nervous tissue leading to the posterior lobe surrounded by a thin cuff of epithelial cells which forms an extension of

* From the Department of Neuroendocrinology, Institute of Psychiatry, Medical Research Council, London, England. Address reprint requests to Dr. Daniel at the Medical Research Council, Institute of Psychiatry, 12th Avenue, London, England. Received for publication, October 15, 1965.

the anterior lobe (In most species a third lobe *pars intermedia* composed of epithelial cells different from those of the anterior lobe is interposed between the anterior and posterior lobes but this is not distinguishable in the human pituitary.)

The posterior lobe has a conventional arterial blood supply obtained from the inferior hypophyseal arteries. The anterior lobe however is not supplied directly by any artery but receives only portal venous blood that is to say blood which has already passed through a first capillary bed (Fig. 1). In man an anastomatic artery, the artery of the trabecula which connects the superior and inferior hypophyseal arterial systems, passes through the anterior lobe but does not supply the epithelial cells.² (Some workers⁴ believe that the human anterior pituitary is supplied by a few arterial twigs but in our view such an arterial supply when it exists at all is so small as to be insignificant. In the rabbit however there is a

fundamental difference from other species in that the anterior lobe has a substantial arterial as well as a portal venous blood supply.)

The portal blood is delivered to the anterior lobe by a number of individual portal vessels and these vessels form two distinct groups, the long and the short portal vessels.^{2, 3} The long portal vessels are those which run down the pituitary stalk but the short portal vessels lie below the level of the free part of the stalk (Fig. 1). On entering the anterior lobe the portal vessels of both groups break up to form the second capillary bed of the portal system, the sinusoids of this lobe. In these freely anastomosing sinusoids the portal blood is carried past the parenchymal cells and finally laden with hormones released by these cells is discharged through short venules at the surface of the anterior lobe into the venous sinuses which surround the pituitary. The venous drainage of the stalk is entirely by way of the

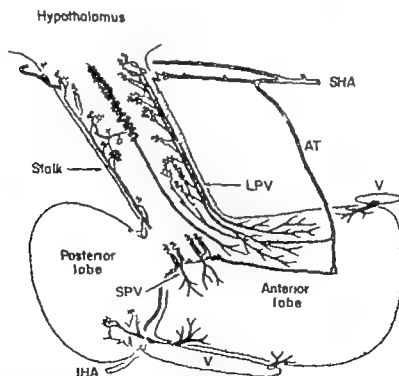


FIG. 1. Diagram of the human pituitary gland and the sagittal plane showing the main features of the blood supply referred to in the text. CLA is the tyled neural tube, white III Long portal vessels, I Short portal vessel, IHA Inferior hypophyseal artery, SHA Superior hypophyseal artery, AT Artery of the trabecula, V Venous sinus adjacent to pituitary.

portal vessels there being no outflow into systemic veins.

The primary capillary beds which feed the two groups of portal vessels both lie in the neural portion of the gland but at different levels. The long portal vessels drain a capillary bed lying in the stalk itself whereas the short portal vessels drain a bed situated lower down. The vessels which make up these primary capillary bed are of characteristic form being looped and convoluted with varying degrees of complexity, some of those in the stalk being of a particularly striking pattern.¹⁰ The capillary bed in the stalk which feeds the long portal vessels is supplied by the superior hypophyseal arteries whereas the bed which drains into the short portal vessels is supplied from the inferior hypophyseal arterial system although in man it also receives some blood (via the artery of the trabecula) from the superior hypophyseal arterial system.

Although the anterior lobe of the pituitary resembles the liver in having a portal circulation it is worth pointing out that some of the well known features of the vascular arrangements and general structure of the liver are not present in the anterior pituitary. For example in the latter there is nothing comparable to the contribution of arterial blood which is distributed to all parts of the liver by the hepatic artery. Furthermore whereas in the liver the sinusoids and cords of parenchymal cells are arranged in countless small self-contained units or lobules of uniform size each of which has its own individual afferent and efferent vessels i.e. small twigs of the widespread trees formed by the portal and hepatic veins,¹⁰ the anterior lobe of the pituitary has no lobular arrangement and nothing even on a small scale that resembles the intraglandular ramifications of the liver's afferent and efferent veins. The whole anterior lobe consists of a single structural unit composed of a continuous network of freely anastomosing sinusoids lined by pericyclic cells and it is this network as a whole that is provided with afferent and efferent vessels. Thus whereas in the liver an individual parenchymal cell whatever its position in the organ is never further from a portal vessel than half the

width of a lobule i.e. less than one millimeter in the anterior pituitary the distance between an individual cell and a portal vessel varies from a few micra to several millimeters depending on whether the cell adjoins a sinusoid at the proximal or the distal end of the entire network. This varying distance implies a difference in the content of the blood bathing the pericyclic cells in different parts of the anterior lobe a fact which may well be of significance in regard to the functional activity of the individual cells.

The existence of the long portal vessels of the pituitary some of which are visible to the naked eye on the surface of the stalk has been known since 1930 when they were first described by Popa and Fielding¹¹ who believed however that they carried blood up the stalk from the pituitary to the hypothalamus¹ since that time direct observations in living animals have shown that the blood in these vessels flows in the opposite direction namely down the stalk to the pituitary.¹² The short portal vessels first described⁷ in 1934 are less conspicuous than their long counterparts since except in the rat⁸ they lie deep within the body of the gland. Each group of portal vessels the long and the short has its own territory of supply in the anterior lobe and these territories are very clearly seen in glands examined a few days after transection of the pituitary stalk an operation which severs the long portal vessels but does not interfere with the circulation through the short portal vessels (see Fig. 1). Such glands show a massive area of necrosis in the central and ventral parts of the anterior lobe⁸ and this infarct demonstrates the very large territory which is dependent for its supply of blood on the long portal vessels e.g. up to 90 per cent of the lobe in man.¹² Similarly the regular survival of small areas along the dorsal border of the lobe shows that these areas are supplied by the short portal vessels.

However not only do the two groups of portal vessels each have their own territories of supply but the distribution of even individual portal vessels appears to be strictly circumscribed. For if a very small lesion is made in the stalk and only

one or two of the long portal vessels e.g. a few on one side are cut or occluded a small ipsilateral infarct regularly develops in the anterior lobe^{12,13} This shows that the territory supplied by a particular portal vessel receives little or no blood from the portal vessels which supply adjacent areas. It seems to be clear therefore that in spite of the free anastomosis of the sinusoids of the anterior lobe there is little if any mixing of blood derived from different portal vessels and that cells in a specific part of the lobe are always fed by the same few portal vessels. This is of special interest because it has been shown that some of the cells of the anterior lobe which are known to secrete a specific type of hormone tend to be concentrated in certain areas of the lobe¹⁴. It may well be that the circumscribed areas of distribution of individual portal vessels and the distinctive grouping of cells in the anterior lobe are related features and that together they form part of a mechanism by which the output of individual hormones from specific cells of the anterior lobe is controlled by small groups of nerve cells in the hypothalamus. For although much of the nerve tract in the pituitary stalk consists of the axons of hypothalamic nerve cells running down to the posterior lobe there is good evidence that the axons of many such nerve cells terminate on the capillaries of the primary bed which feed the portal vessels¹⁵. It is tempting therefore to postulate that specific groups of neurons in a hypothalamic nucleus are linked via the capillary loops draining into particular portal vessels with specific groups of cells in the anterior lobe and thus control the secretion of those particular cells¹⁶. That the normal functions of cells of the anterior lobe are largely maintained by neurohumoral stimuli received directly from the hypothalamus is well seen when the lobe is deprived of such stimuli as for example by section of the pituitary stalk and the insertion of a plate to form a permanent barrier between its cut ends. With the passage of time after this operation the cells in the areas which escape infarction become very small^{17,18} and there is a severe loss or even a complete disappearance of the intracytoplasmic granules which are

normally seen and indicate hormonal activity^{19,20}. The altered appearance of the cells is presumably due to the change in their environmental conditions. For although these cells continue to receive blood from the short portal vessels the latter are now draining a capillary bed which has been denervated (since the axons which end on this bed have been cut in the stalk) and consequently the blood which these vessels carry no longer contains the neurohumors of hypothalamic origin which it normally transports.

Although all of the details of the way in which hypothalamic control of the anterior pituitary is achieved are not yet known one factor is undoubtedly essential namely the presence of intact connections vascular and neural between brain and gland. When these connections have been permanently interrupted as by section of the stalk and the insertion of a plate not only is the pituitary gland itself affected but striking changes also occur elsewhere in the body²¹. For example there is a marked retardation of bodily growth in young animals and individual organs such as the heart, kidneys, liver and intestines all fail to grow to their normal size. Metabolic disturbances are pronounced and may include severe hypoglycemia²². Atrophic changes occur in the organs under pituitary control the target organs most severely affected being the gonads, the accessory sex organs and the cortex of the adrenal glands. Many of the remote changes caused by section of the stalk are indeed essentially equivalent to those observed after actual removal of the pituitary^{23,24}.

The posterior lobe is equally dependent for its normal functioning on having an intact connection with the hypothalamus. In this case the connection is entirely a neural one, the nerve tract running down in the pituitary stalk. When the pituitary stalk is cut this connection is severed of course and as a result of its denervation the posterior lobe atrophies although its blood supply remains intact^{25,26}. The immediate effect of this denervation is to induce a severe diabetes insipidus a result which shows clearly that the output of antidiuretic hormone from the posterior lobe is under hypothalamic control. A

similar polyuria is not infrequently seen in cases of head injury and this is due to the nerve tract to the posterior lobe having been damaged.²²

On the pathologic side an understanding of the detailed vascular anatomy of the pituitary particularly as demonstrated by the effect of section of the stalk provides an explanation for the changes seen in the gland in cases of postpartum necrosis of the anterior pituitary. For the infarct seen in the first few days after section of the stalk is so remarkably similar in extent and position to the lesion found in acute cases of postpartum pituitary necrosis²⁴ that one must assume that the necrosis occurring postpartum is due to a failure of the circulation through the long portal vessels of the stalk caused by some factor associated with the abnormal termination of the pregnancy. Similarly a failure of the circulation through this same group of portal vessels possibly associated with a low blood pressure must also be the cause of the massive anterior pituitary necrosis which is occasionally found in patients suffering from diabetes mellitus. That the flow of blood through the portal vessels in the stalk can vary very considerably has been shown by Worthington²⁵ who watched these vessels directly in living animals observing the effects of various distant stimuli and drugs. However much still remains to be discovered about the flow of blood through the pituitary and the various influences to which the circulation of this vital organ is subject both in health and in disease but the small size of the gland and its inaccessible situation make the investigation of these problems unusually difficult.

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The electrocardiogram of young Nigerians

O. Seriki MB MFCPEd
A. J. Smith BV MRCP*
Lagos, Nigeria

During a survey of arterial hypertension in the Lagos University Teaching Hospital, Nigeria,¹ it became apparent that no criteria exist for the interpretation of the electrocardiogram of the Nigerian subject apart from those found in European or American texts.

Several observers have recorded variants of the normal electrocardiogram in Africans and in those of African descent. Trowell² describing two of these comments that in most parts of Africa clinicians have studied the ECG in a large number of Africans and have been unable to detect the abnormalities (sic) that occur in South Africa.

It is unlikely that these abnormalities occur or occur commonly in other countries in Africa. However there have been reports of similar variants not only from South Africa³ but also from Uganda in East Africa.⁴

Peculiarities of the ST segment in precordial leads have been recorded in normal American Negroes^{5,6} although Phillips and Burch⁷ comment little on variations in the electrocardiographic pattern in the course of their review of racial differences in the incidence and presentation of cardiovascular disease.

This paper records our findings in healthy West African children and young adults in Lagos, Nigeria.

Material

The first 100 electrocardiographic tracings were recorded from 50 female student nurses (mean age of 19.3 years) and 50 male medical students (mean age of 24.0 years). All had been medically examined and found to be healthy on admission to either nursing or medical school and none had a past history of rheumatic fever or symptoms suggesting a cardiac lesion. The heart was examined and the blood pressure measured after the electrocardiogram had been recorded and chest x-ray films were available for all of the subjects.

Electrocardiograms from 202 school children 8 to 16 years of age were recorded in two local schools. The numbers of boys and girls in each age group are shown in Table 1. It was not possible to investigate each of these children in detail but examination of the cardiovascular system re-

Table 1 Age and sex distribution of 202 Nigerian school children

Age (yr)	Male	Female
8-9		
10-11	40	40
12-13	44	16
14-16	50	—
	12	—

veiled no abnormality in any of them. A standard 12 lead electrocardiogram was taken with the subject lying comfortably on a couch. A Phillips Cardiopan 1 machine was used although some of the electrocardiographic variants were recorded again when a Cambridge direct writing, portable apparatus was used in order to exclude mechanical artefact as a source of the unusual tracings.

Results

All of the subjects were normal on examination with blood pressures well within the accepted range. All chest x-ray films were normal.

Most of the standard electrocardiographic measurements conformed to the accepted American or European pattern. In particular the duration of the P-R and Q-T intervals, the length of the QRS complex and the height of the I and T waves corresponded well with findings obtained in other countries.

Electrocardiograms from young adults

I-AXIS INCLINATION. Mean frontal plane axis was calculated from the standard triaxial reference system. A frequency/distribution diagram was drawn for each group of students separately and in combination and is shown in Fig. 1. This is within normal limits.

ELEVATION OF ST SEGMENT. Among the 50 student nurses no electrocardiogram showed elevation of the ST segment by more than 2 mm from the isoelectric line in any lead. In the male students ST segment elevation in excess of 2 mm with a concave form ending in a tall positive T wave was common occurring in 17 cases (34 per cent) in 12 recorded lead V₁. It appeared less frequently in leads V₂ and V₄ and was not apparent in standard or augmented limb leads.

This elevation was persistent over a period of 6 months and was not affected by exercise in the 3 subjects in whom this was studied. A typical electrocardiogram showing this feature is reproduced in Fig. 2. This corresponds closely with the variants described by Goldman⁸ in American and by Litten II⁹ by Crislin¹⁰ in South Africa.

The differing sex incidence of this variant might be related to age (the medical stu-



Fig. 1. Frequency/distribution diagram of axis deviation (mean frontal plane) in 50 male student (*top*), 50 female student (*center*) and both groups in combination (*bottom*).

dents were on an average 3 years older than the nurses) but was also reported by Crislin.¹⁰ In his series 27 per cent of 200 male patients showed ST segment elevation although it was present in only 2 (4 per cent) of 50 female nurses.

In our series the frequency of ST segment elevation bore no relationship to tribal origin or to hemoglobin genotype. (Twenty per cent of the subjects were of AS genotype, the rest were AA—roughly the same proportion as that existing in the general population in Nigeria.)

3. INVERTED OR BIPHASIC T WAVES

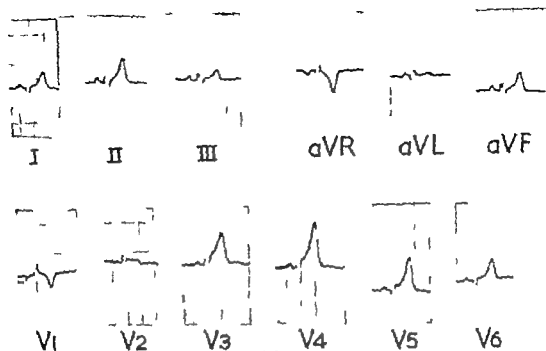


Fig. 2 Electrocardiogram of healthy male Nigerian student showing elevation of S-T segment in precordial leads

Inverted or biphasic T waves were often found in the right precordial leads (in 92 per cent of cases in Lead V_1 and in 51 per cent in Lead V_2). The T waves were frequently deeply inverted and asymmetrical with long sloping proximal limbs and relatively sharp distal ascent to the isoelectric line. Inverted T waves in Leads V_1 and V_2 are not uncommon outside Africa but it is unusual to find inversion extending to Leads V_3 and V_4 . In this series 7 subjects had inverted T waves in either Lead V_3 or Lead V_4 or in both.

4. LEFT VENTRICULAR HYPERTROPHY. In 3 normotensive subjects with no signs of left ventricular hypertrophy the combined magnitude of R_{V5} and S_{V1} was well in excess of 40 mm. In young people this may occasionally have no significance but it is included here since both Crusan² and Somers and Ripkin³ recorded this pattern in normal subjects from other parts of Africa.

Electrocardiograms from school children. No additional variants were found in these subjects and they conformed to the standard pattern in most respects.

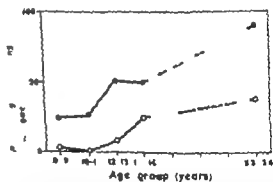


Fig. 3 Percentage incidence of electrocardiograms showing S-T segment elevation in the age group examined. Solid-dot curve: Elevation in any lead of less than 2 mm. Open-dot curve: Elevation in any lead of more than 2 mm.

1. S-T segment elevation. The percentage incidence of S-T segment elevation of 1 and 2 mm or more in any lead is plotted against age in Fig. 3. It can be seen that the incidence of elevation of the S-T segment increases with age. Although it was not possible to examine many girls over the age of 11, S-T segment elevation

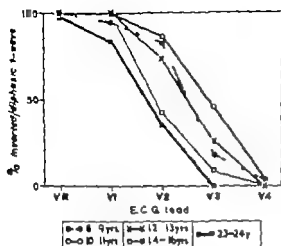


Fig. 4 Percentage incidence of inverted/biphasic T waves in right and mid precordial leads related to age in 302 normal Nigerian subjects

was notably more frequent in boys below that age

2 INVERTED OR BIPHASIC T WAVES
Inverted or biphasic T waves were commonly seen in precordial leads on the right side. The percentage incidence in each of five leads is related to the age of the subject in Fig. 4. It can be seen that this pattern becomes less prominent with increasing age after 11 years.

Discussion

Our findings in Nigeria are similar to those from South and East Africa and from American Negro populations. The particular variants described have been recorded previously by clinicians working in Africa but not in so far as we know from the West African coast.

The significance of these patterns is obscure. Elevation of ST segments which may cause considerable diagnostic confusion⁷ is apparently acquired during late childhood and adolescence and is more prominent in males than females. It seems to be unlikely that it is related to cardiac disease since all of our subjects were healthy and gave no history of previous illness apart from recurrent pyrexia attributed to malaria and occasional gastroenteritis.

On the other hand inversion of T waves in right precordial leads becomes less

common with increasing years. It has been described as the persistence of a juvenile form in American Negroes^{10,11} and our findings support this suggestion.

The importance of racial variants in the electrocardiogram and their confusion with truly abnormal tracings has been stressed by Goldman.¹² It seems to be likely that the patterns which we have found in Nigeria will be found among Africans and those of African descent whenever systematic search is made for them.

Summary

Examination of the electrocardiograms of 100 students and 202 school children in Lagos, Nigeria, revealed a high incidence of ST segment elevation in precordial leads increasing with age and occurring more commonly in males.

Biphasic or inverted T waves were found commonly in precordial leads on the right side occasionally extending as far as Lead V₄. This is less common in older subjects and may represent a persistence into young adult life of a juvenile form.

These normal appearances deserve wider recognition in order to prevent confusion in interpretation of the electrocardiogram.

We would like to thank the student doctors and teachers at the local schools and to acknowledge the help given by Dr T. Okoroafor, Staff Medical Officer, who made available medical records, x-ray films and hematological investigations. Professor G. L. Moseleson gave helpful advice and the British Heart Foundation provided financial support for this and related investigations carried out in the Department. Figures were prepared by the Department of Medical Illustration, University of Lagos Medical School.

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Congenital aortic sinus aneurysms

With particular reference to dissection of the interventricular septum

Altan Onat MD MS FCCP

Orkan Ersoylu MD

Aykan Kanuni MD

Tolga B Aykan MD

Istanbul Turkey

Aneurysms of the aortic sinus of Valvula may be congenital syphilitic or due to bacterial endocarditis. The latter two etiological types appear to be decreasing in frequency. Congenital aneurysms of the aortic sinuses were considered to be a rare entity, yet the sharply increasing number of cases reported in the literature during the past quarter century indicates that this lesion is more common than was formerly believed. Sakakibara and Konno¹ stated that after the first detailed description of this entity by Thurnam in 1840 only 18 similar cases were reported in the subsequent 100 years in the following two decades however 19 and 51 cases were reported adding up to a total of 88 cases by 1960. Since then the tendency to geometric increase has not ceased. We were able to trace in the literature 82 additional new cases of congenital aortic sinus aneurysm²⁻¹¹ in the 4 years up to 1964.

A congenital aortic sinus aneurysm protrudes in a diverticular fashion and commonly penetrates into a low pressure area usually into the right ventricle or right atrium rarely into the pulmonary artery pericardial sac left atrium or left

ventricle. However aorticocardiac fistulas involving a large aneurysm lying within the interventricular septum have rarely been recorded and have not received adequate attention. The following report concerns 2 patients in whom a fistulous communication existed between the right coronary sinus and a large aneurysm occupying primarily the muscular portion of the interventricular septum. Secondary penetration occurred into the right ventricular outflow tract and into the left ventricle respectively.

Report of cases

Case 1. A 26 year-old farmer was admitted to our Department on March 11 1963 with the chief complaint of exertional dyspnea on inspiration and swelling of the ankles of 1½ months duration. He had been active in his work on the farm and free from complaints until the onset of his present illness. He stated that he had been found fit during a medical examination in 1939 for military service which he performed fully for 2 years. His complaint started without an abrupt onset sometime late in January 1963 when progressively increasing exertional dyspnea and palpitations were first noted followed by dyspnea at rest and more recently by an aching pain in the right hypochondrium and swelling of the lower extremities.

On physical examination the patient appeared to be dyspneic. The neck veins were distended and

a moderate degree of soft pitting bilateral pretibial edema was present. The pulse was of collapsing type and the blood pressure measured 135/50 mm Hg. There was a slightly increased left ventricular activity and a moderate precordial heave. Auscultation revealed frequent premature beats and a superficially appearing Grade 6/6 continuous murmur with systolic and diastolic accentuation. The murmur had its greatest intensity in the third intercostal space to the left of the sternum and was transmitted to the second and fourth left intercostal spaces. A continuous thrill was associated which was more intense in diastole. The liver was enlarged 3 fingerbreadths below the right costal margin, was tender and disclosed systolic pulsation. The patient remained afebrile throughout the period of observation. The phonocardiogram (Fig 1) confirmed that the continuous murmur exhibited a systolic and a diastolic peak of intensity with greater accentuation of the diastolic murmur. The electrocardiogram showed frequent multifocal premature ventricular beats. A focal intraventricular block was present in which a wide angle could be traced the mean interval (-60 degrees slightly anterior) and terminal (-10 degrees posterior) 0.04 second QRS vectors. Signs of ventricular hypertrophy were absent. X-ray films of the chest and fluoroscopy revealed a moderate enlargement of both ventricles and an increase in long vascular markings. The jugular venous pressure measured 24 cm H₂O. Blood counts, sedimentation rate, urinalysis and serum electrolytes were within normal limits. Serologic tests for syphilis and blood cultures remained negative.

Evidently the patient had an aortic leakage with a left to right shunt. In view of the rapid development of congestive failure in this patient who had

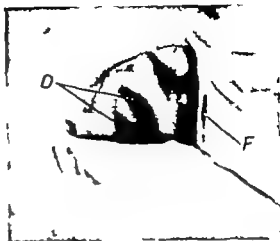


Fig 2 Case 1. Close up of the right aortic sinus of Valachi shows the openings (O) communicating with the aneurysm and the fenestrations (F) of the cusp.

shown no previous cardiac disability and the superficial continuous murmur with two peaks of intensity a presumptive diagnosis of aortic sinus aneurysm with rupture into the right ventricular outflow tract was made. The patient was put on a low sodium diet and bed rest. Cephadril and low doses of chlorothalidone were given in preparation for retrograde aortography and subsequent attempt at surgical repair. Signs of congestive failure diminished but myocardial irritability persisted as evidenced by relatively frequent ventricular premature beats. On March 21 the night before the scheduled aortography the patient died suddenly, presumably from ventricular fibrillation or possibly from cardiac arrest secondary to complete heart block.

Pathology. The heart weighed 400 grams. Both ventricles were dilated; the right ventricle had a maximal thickness of 6 mm and the left 5 mm. The right aortic cusp exhibited two small fenestrations (Fig 2). In the central third of the right coronary sinus there were two openings which measured 6 by 9 mm and 10 by 10 mm (Fig 1). A third opening 2 mm in diameter existed inferiorly below. All three openings communicated with an aneurysm measuring 6.6 by 6.4 by 3.5 cm in size occupying in part the membranous interventricular septum and the upper portion of the muscular septum and partly extending into the lateral wall of the left ventricle (Fig 3). The aneurysm had a glistening lining. Neither the aneurysm nor the aortic valve showed any vegetations. The portion of the aneurysm just below the right coronary sinus was separated from the left ventricular cavity by a fibromuscular wall 2 to 3 mm in thickness. The aneurysm bulged into the outflow tract of the right ventricle (an area extending from just below the pulmonary valve down to the beginning of the papillary muscle of the septal leaflet of the tricuspid valve). On the wall of the aneurysm a 6 mm

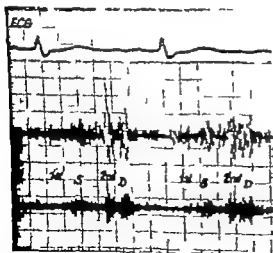


Fig 1 Case 1. Phonocardiogram recorded in the third left intercostal space demonstrates a to-and-fro type of murmur with a systolic (S) and diastolic (D) peak of intensity.



Fig 3 Case 1 View from the left ventricle. Congenital aneurysm (1) of the right coronary sinus (RCS) lying within the muscular portion of the interventricular septum (VS) and partly extending into the anterior wall of the left ventricle (LV).



Fig 4 Case 1 View from the left ventricle. The aneurysm (1) was opening at the crista supraventricularis (CS) in communication with the aneurysm as indicated by the arrow. Three further openings (O) are situated just below P. Pulmonary valve.

4 by 2 mm) existed at the crista supraventricularis and three additional fistulas (measuring 6 by 6 2 by 2 and 9 by 4 mm) just below the supraventricular crest (Fig 4). The coronary arteries as well as the lining of the aorta and pulmonary artery presented no abnormalities.

The rest of the necropsy disclosed congestion of the lungs, liver and kidneys. A cancerous tuberculosis of the pancreas and tuberculous peripancreatic lymph nodes were found.

HISTOLOGIC EXAMINATION Histologic examination of the aneurysmal wall revealed a layer of fibrous tissue below which existed connective tissue interspersed with lymphocytes, plasma cells, histiocytes and newly formed capillaries. The neighboring myocardium demonstrated scattered fibrous areas and inflammatory areas consisting of mononuclear cellular infiltration. Inflammatory cellular infiltration was not seen in areas of the myocardium remote from the aneurysm.

Case 2 The clinical information available on this patient is limited. A 32-year-old male laborer, he was seen elsewhere as an outpatient in June 1961 because of dyspnea and palpitation. The apex beat was palpated at the sixth left intercostal space. A fingerbreadth outflow in the mid-clavicular line. An intense systolic murmur was heard both at the left parasternal area and at the apex. An electrocardiogram showed right bundle branch block. The cardiac size was increased roentgenographically. Repeated follow-up examinations disclosed the development of atrioventricular dissociation in February 1963. When he was hospitalized in April 1963 because of a increase in dyspnea and palpitation his pulse rate was 40 per minute and blood pressure 120/60 mm Hg. A mild diastolic murmur was noted at

addition to the previous cardiac findings. The edge of the liver was palpable 2 fingerbreadths below the costal margin. Serologic tests for syphilis were negative. Blood leukocyte count and sedimentation rate remained normal and urinalysis was negative as they were during his previous visits. Throughout his stay in the hospital the patient remained afebrile. He complained of retrosternal discomfort and exhibited paranoid ideas. One day prior to his death he experienced two episodes of syncope associated with urinary incontinence. On May 24 the patient died.

HISTOPATHOLOGY There was hypertrophy and marked dilatation of the left ventricle which had a wall thickness of 20 mm. The right ventricle showed marked hypertrophy and dilatation; its wall measured 7 mm. The right aortic cusp exhibited only a narrow rim of cuspid tissue (hemorrhagic necrosis) (Fig. 5). The right coronary sinus presented as a large pouch which was distended by thrombus. This pouch extended into a large cavity which measured 7 by 7 by 6 cm and occupied the inter-ventricular septum. The aneurysmal cavity was full of thrombi of mixed type. It extended from the aortic annulus fibrous down to a level 8 cm away from the apex and from the anterior wall of the septum to the posterior aortic cusp. The aneurysm bulged toward the pulmonary cones obstructing its bases considerably. Posteriorly it protruded toward the base of the right atrium narrowing it at the level of the septal leaflet of the tricuspid



Fig. 5 Case 2 Congenital aneurysm of the right coronary sinus with intramural rupture and secondary penetration (R) into the left ventricle (LI). Only a narrow rim of the right aortic cusp (C) exists. Below this cusp is a large area of endocardial fibrosis covering the large aneurysm at the muscular portion of the inter-ventricular septum (S) and in the middle of which is a small area of hemorrhagic necrosis (V).



Fig. 6 Case 2 Right ventricular view. The anterior (T4) and the posterior (TP) tricuspid leaflets are visible and (1) the site of the septal leaflet protrusion of the aneurysmal wall is apparent. The septal leaflet is missing presumably secondary to pressure of the aneurysmal protrusion and fusion with the surface of the aneurysm. Chordae tendineae (Ch) extending to the absent septal leaflet are barely visible.

valve. The septal leaflet was absent presumably fused to the surface of the aneurysmal protrusion which presented marked endocardial thickening. Remnants of a few chordae tendineae extended in this direction (Fig. 6). The endocardium of the left ventricle was markedly thickened in an area lying below the right aortic cusp and anterior to it. Here a fistulous opening communicated with an extension of the aneurysmal cavity in the anterior wall of the left ventricle. Farther below an area of hemorrhagic necrosis was noted in a region in which the wall of the aneurysmal cavity was very thin (Fig. 5).

HISTOLOGIC EXAMINATION Histologic examination of the aneurysmal wall and the neighboring myocardium revealed extensive fibrosis with loosely diffuse and focal inflammatory reaction accompanied by hemorrhage, and very few capillaries. Small fibrous areas were present in other regions of the myocardium. The tip of the major papillary muscle of the left ventricle demonstrated larger fibrous areas. The lungs disclosed bilateral pneumonia, old pleural thickening and adhesions. The liver was markedly edematous. The kidneys, adrenal gland, and spleen as well as other organs and mucous membranes showed no other changes and edema.

Discussion

In the majority of cases of congenital aortic sinus aneurysm the lesion assumes the form of a diverticular protrusion into a cardiac cavity. The two cases presented in this paper were unusual in that in each instance a large aneurysm was contained within the muscular portion of the ventricular septum. It has been pointed out^{1,14} that congenital aneurysms are small and are almost always confined to the right coronary sinus and adjacent two thirds of the noncoronary sinus and that they commonly rupture to form aorticocardiac fistulas. On the other hand acquired aneurysms may arise from any of the aortic sinuses, are large in size, tend to extend upward and often rupture outside the heart. Although the involvement of the ventricular septum by a large aneurysm may lead one to suspect the presence of an acquired cause, there was no clinical or autopsy evidence of an acquired cause in our cases. Consequently both aneurysms may be justly considered to be congenital in origin. Gibbs and Harris⁶ described the case of a patient who had a congenital aneurysm of the left and right coronary sinuses. The aneurysm dissected the ventricular septum forming a large cavity, the lower portion of which was described to be in the muscular portion of the septum. There was no perforation into a cavity and the patient died from aortic regurgitation and cardiac failure due to congenital absence of the right aortic valve cusp. Individual cases of congenital aortic sinus aneurysm with intramural rupture and dissection of the membranous portion of the interventricular septum have also been described by Linn¹⁷, Warthen¹⁸, Lee¹⁹, Orban and Mostofi²⁰ and Kay.¹ Secondary penetration into the left atrium occurred in one of these cases²¹ and into the left ventricle in two.^{17,18} Sakakibara and Konno² suspected that this type of aneurysm developed after intramural rupture of a congenital aneurysm with subsequent formation of a hematoma and organization. They considered this variety of case to be representative of a pseudoaneurysm. The pre-existence of an additional localized area of fragile tissue at this portion of the interventricular septum is postulated to explain the intramural rupture of the

aneurysm instead of protrusion into a cardiac cavity.

Clinically aneurysms which dissect the ventricular septum present few distinctive features as compared to those which do not. Worthiness of emphasis is the more frequent occurrence of atrioventricular conduction disturbances. Although A-V block, A-V nodal rhythm and right bundle branch block have been reported occasionally in cases of congenital aortic sinus aneurysm^{1,18,19} particularly in those instances in which the aneurysm protrudes or penetrates just above or below the tricuspid valve, conduction defects appear to be very common in cases of aneurysm involving the ventricular septum. Focal intraventricular block occurred in Case 1 and complete atrioventricular dissociation in Case 2. These changes were presumably due to the encroachment of the aneurysm on the septum where the specialized conduction system is most densely concentrated. In the case of Lee and associates¹⁹ death resulted from complete heart block which was believed to be due to hemorrhage into and inflammation of the conduction system. Bundle branch block was observed in the cases reported by Warthen¹⁸ and Gibbs and Harris.⁶

In the two cases presented herein the aneurysms dissecting the ventricular septum penetrated into the outflow tract of the right ventricle and into the left ventricle respectively. In this connection we have attempted to review the cases of congenital aortic sinus aneurysms reported in the world literature since the last comprehensive survey¹ of this field appeared in the English literature. The sites of origin and penetration of the aneurysms are listed in Table 1. The left ventricle is a rare site of termination, namely, in one⁶ out of 67 instances of ruptured aneurysms.⁶ Although congenital aneurysms of the aortic sinuses penetrate far more frequently into the right cardiac cavities, such a predilection is not observed in the limited number of cases with dissection of the ventricular septum. Reasons of topographic proximity should account for this difference.

Table 1 Sites of origin and penetration of congenital aortic sinus aneurysms in 77 cases*

Site of origin	Number of cases		Site of termination	Number of cases
	Unruptured	Ruptured		
Right coronary sinus	4	47	Right ventricular outflow tract	24
			Right ventricular inflow tract	10
			Right atrium	11
			Pulmonary artery	2
Noncoronary sinus	1	13	Right atrium	11
			Right ventricle	3
			Left ventricle	1
Left coronary sinus	1	4	Right atrium	3
			Left atrium	1
Unknown		1	Right atrium	1
Right and noncoronary sinuses	2			
Right and left coronary sinuses	1			
All three coronary sinuses	1			
Total	10	67		67

* Cases 1 died prior to surgery and were totally perforated in 1960. In the case of the French authors have been included. The names of the cases are given in the text. The names of the cases are given in the text.

Unless other congenital cardiac anomalies are associated an aneurysm of the sinus of Valsalva remains silent until it ruptures or leads to bacterial endocarditis. Coronary insufficiency with myocardial infarction¹⁸ conduction disturbances functional pulmonary stenosis¹⁹ tricuspid insufficiency obstruction to tricuspid inlet and pulmonary emboli originating in the right atrium²¹ have been recorded as rare complications of unruptured aortic sinus aneurysms. The development of aortic regurgitation is a more frequent observation.²² The basis for regurgitation in our second case was loss of substance exclusively of the right anterior aortic cusp. This was thought to be due to the mechanical effects of the turbulent blood stream on this cusp which had been distended by thrombus in that sinus and which protruded toward the orifice. Tricuspid insufficiency has been noted occasionally in cases of ruptured aneurysm of the aortic sinus even in the absence of right ventricular failure. However the observation in Case 2 namely absence of the septal leaflet of the tricuspid valve presumably

secondary to fusion with the surface of the aneurysmal protrusion has not been previously recorded to our knowledge.

In view of the known risks to which patients with ruptured aortic sinus aneurysm are exposed and their poor prognosis in general surgery is recommended in each case and is a matter of urgency in the more severe cases in patients with heart failure.² Surgical treatment has progressed to complete occlusion of the fistula and reconstruction of the aortic root using extra corporeal circulation alone or combined with hypothermia. The results have been fairly satisfactory. However surgical correction of an aneurysm lying within the muscular portion of the interventricular septum entails evident and major problems. In this instance the usual procedure of closure by suturing and placing a patch for reinforcement of the ruptured area would be unsatisfactory for a long period of time since the underlying aneurysmal cavity would persist and offer no support. A more radical operation namely total replacement of the aortic valve might be needed and prove to be more satisfactory.

This would involve closure of the fistula from the aortic side its reinforcement by the cuff of the prosthesis and correction of the frequently associated aortic regurgitation in addition to simple closure of the fistula from the right or left ventricular side. A reopening of the fistula might thereby be prevented even though the aneurysmal cavity is left alone.

Summary

Two cases of ruptured congenital aneurysm of the sinus of Valsalva have been reported in which a large aneurysm dissected the muscular portion of the inter-ventricular septum. Penetration through the crista supraventricularis occurred in one case and into the left ventricle in the other case. In the latter patient the septal leaflet of the tricuspid valve was absent because of fusion with the protruded aneurysmal surface and aortic regurgitation was associated. Conduction disturbances were present in both cases. The relationship of congenital aortic sinus aneurysms in general to those involving the ventricular septum was discussed. Problems pertaining to surgical correction of aneurysms of the latter type were pointed out.

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Hematocrit, plasma protein, plasma volume, and viscosity in early hypertensive disease

Gosta Tibblin MD*

S E Bergentz MD

J Bjure MD

L Nilhelmsen MD

Goteborg Sweden

There are two major factors which determine the level of the arterial blood pressure namely the volume of blood flow through the arteries per unit of time and the resistance to the blood flow offered by the arterioles and the capillaries. The circulating blood volume and the blood viscosity have been considered to be of secondary importance.

In 1905 Gaisbock¹ applied the term polycythemia hypertonica to a group of hypertensive patients with elevated red blood cell count. Reports of so-called benign polycythemia have been published by Lawrence and Berlin² and Russell and Conley.³

A positive and significant correlation between hematocrit and diastolic blood pressure has been reported by McDonough and associates.⁴ In the Men of 1913—a population study of 973 men all born in 1913—an increased hematocrit and an elevated total plasma protein were found in subjects with diastolic blood pressure ≥ 100 mm Hg.

The purpose of the present study was to investigate in more detail this apparent tendency to hemoconcentration in early

hypertensive disease in a series of hypertensive individuals taken from the subjects investigated in that study¹⁴ and to use as controls normotensive individuals from the same population.

Material

The Men of 1913 Study is a population study of 973 men all born during 1913 and living in Goteborg Sweden. The prime interest was centered upon the early manifestations of chronic disease. During 1963 88 per cent of the subjects selected at random were examined at this hospital. The examination was a 4-hour study of the individual's state of health using the personnel and technical resources of the hospital. Among the variables investigated as being of special interest to the present study were the following: hematocrit (Wifug Stockholm), total plasma protein (Biuret), blood pressure, eyeground (examination by an ophthalmologist), heart volume, electrocardiogram, kidney function and skinfold thickness.

During the autumn of 1964 the subjects with elevated systolic and diastolic blood pressure were re-examined. The hyperten-

From the First Medical Service, First Surgical Service and the Department of Clinical Pharmacology, Sahlgrenska Hospital, University of Göteborg, Göteborg, Sweden.

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Address reprint requests to Dr. Gosta Tibblin, First Medical Service, Sahlgrenska Hospital, S-413 45, Göteborg, Sweden.

Table 1 Blood pressure, hematocrit, total serum proteins and subscapular skinfold in the normotensive and hypertensive subjects when examined in 1963 (Göteborg study 1963)

Subjects	Systolic blood pressure	Diastolic blood pressure	Hematocrit	Serum protein	Subscapular skinfold
Normotensive					
n	124	80	43.3	7.01	13
\bar{x}	11	8	4.7	0.20	3
s	11	11	11	11	11
Hypertensive					
n	181	112	43.8	7.29	23
\bar{x}	14	10	2.2	0.14	11
s	14	14	14	14	14
p	<0.001	<0.001	<0.05	<0.05	<0.01

d = standard deviation; s = standard deviation of subject

sive group of the present study was selected from these subjects. The criteria used in choosing the hypertensive subjects were untreated individuals with blood pressure of $\geq 160/95$ mm Hg and hypertensive changes in eyeground (attenuated arterioles and/or changes in caliber). Sixteen subjects fulfilled these criteria and 14 took part in the study. From the normotensive population with out heart disease examined in 1963, 14 men were selected at random and asked to take part in the study as controls and of these 12 men accepted. Since complete study of one of these could not be made, this subject was subsequently excluded from the control material.

Blood pressure, hematocrit, total serum proteins and subscapular skinfold values for these 14 hypertensive and 12 normotensive subjects at the time of the 1963 examination are given in Table 1.

The total serum proteins and subscapular skinfold were significantly increased in the hypertensive group. In the hypertensive group the mean value for the hematocrit was 45.5 per cent as compared with 43.3 for the normotensive group ($p < 0.05$).

It can be seen therefore that it was possible to investigate two groups from the same population of the same age and sex. The hypertensive group can be considered to be representative of the untreated hypertensive individuals and the control group to be representative of the normo-

tensive subjects in the same population. The subjects in both groups were without complicating diseases such as anemia, heart failure, kidney diseases or pulmonary diseases. Heart volume, kidney function and respiratory function were normal in all subjects. All subjects except one hypertensive individual were working full time when studied in 1964. The subjects in the hypertensive group were in the early stage of manifest hypertensive disease with hypertensive changes in eyeground but without severe manifestations from other organs.

Procedure

All subjects were studied during the months of October and November 1964 and always at the same time of the day. About 4 hours had elapsed since their last meal. After arrival at the laboratory they were allowed to rest in the recumbent position for about 30 minutes. The investigation was performed with the subject in the supine position on a table with his feet on the pedals of a bicycle ergometer. The pedals were placed 30 cm above the level of the table.

A polyethylene catheter was introduced into an intercutaneous vein by means of a modified Seldinger technique¹² and all samples of blood were taken through this catheter without aspiration. During the first 20 minutes after the injection of 125 I-albumin resting values were obtained. At

21 minutes the subjects started to work with a load of 600 kilogram meters per minute (kg M/min) for 14 minutes in all subjects except one for whom a lower work load (400 kg M/min) had to be chosen.

Methods

Blood pressures were measured with a sphygmomanometer cuff on the right arm. Diastolic blood pressure was taken as that value at which the heart sounds had completely disappeared. Mean blood pressure was estimated as diastolic pressure plus one third of pulse pressure. Heart rate was obtained from the ECG. Venous hematocrit was determined in a capillary hematocrit centrifuge at 12 000 rpm for 10 minutes (Kemla Stockholm). The mean value of two samples was used. The total plasma protein content was determined by the Biuret method. The plasma protein fractions were analyzed by paper electrophoresis in a TRIS-buffer pH 8.9 (Aranson and Gronvall). Plasma volume was measured with 125 I human serum albumin. Usually about 10 μ Ci was injected (time 0) through the catheter in the brachial vein. After thorough washing of the catheter with heparin saline samples of blood were taken from the same catheter at 5, 10, 15 and 20 minutes after injection. The plasma radioactivity of these samples was plotted semilogarithmically against time and a

straight line was fitted to these points. The radioactivity at zero time was used to estimate the plasma volume. During exercise samples for the determination of radioactivity were taken at 26, 30 and 34 minutes after injection. The plasma volume during exercise at these intervals was calculated by multiplying the plasma volume at rest by the ratio of expected plasma activity over observed plasma activity at each interval. The viscosity of whole blood and plasma was determined in a Brookfield synchro-lectric viscometer model LVT equipped with a special adapter for small samples of blood. The samples of blood were withdrawn in dry heparinized tubes. Determinations were made in a water bath at 37°C and the viscosity was calibrated against distilled water under identical conditions. The determinations were always made at four different rotational speeds: 6, 12, 30 and 60 rpm representing the following shear rates: 23, 46, 115 and 230 inverse seconds.

Results

From the 1963 study Tables II and III present the hematocrit and total serum protein values for the whole material (825 subjects) from the 1963 examination. To avoid the influence of obesity on hematocrit and total serum proteins the series is divided into quartiles according

Table II Hematocrit in different quartiles of subscapular skinfold for subjects with diastolic blood pressure < 100 mm Hg and subjects with blood pressure \geq 100 mm Hg in the popliteal study 1963 (n = 825)

	1st quartile 5-19 mm	2nd quartile 19-24 mm	3rd quartile 25-28 mm	4th quartile 29-30 mm
Diastolic blood pressure < 100 mm Hg				
x	44.3	44.7	45.1	44.5
s	3.2	3.3	3.4	3.1
n	185	189	147	108
Diastolic blood pressure > 100 mm Hg				
x	45.7	46.0	45.2	45.5
s	3.5	2.5	3.1	3.0
n	38	54	53	77
P	< 0.05	< 0.005	> 0.05	< 0.05

Table III Total serum proteins in different quartiles of subscapular skinfold for subjects with diastolic blood pressure ≤ 100 mm Hg and subjects with blood pressure ≥ 100 mm Hg in the population study 1963 ($n = 849$)

	1st quartile area 5-10 mm	2nd quartile area 11-14 mm	3rd quartile area 15-18 mm	4th quartile area 19-40 mm
Diastolic blood pressure ≤ 100 mm Hg				
\bar{x}	7.06	7.09	7.15	7.08
s	0.32	0.46	0.41	0.44
n	184	189	146	109
Diastolic blood pressure ≥ 100 mm Hg				
\bar{x}	7.26	7.17	7.24	7.25
s	0.48	0.49	0.46	0.48
n	28	54	53	77
p	< 0.01	> 0.05	> 0.05	< 0.01

to subscapular skinfold values. The subjects with elevated diastolic blood pressure had significantly higher hematocrits in all groups except one. The mean values for the total serum proteins were higher in all groups for the subjects with elevated diastolic pressure and the differences were significant in two groups. There was no tendency to higher differences in hematocrit and total serum proteins in the more obese subjects.

From the present study 1964

ANTHROPOMETRIC DATA Anthropometric data are given in Table IV. There was no

significant difference in height, weight and body surface area between the two groups.

BLOOD PRESSURE Blood pressure reactions are given in Table V and illustrated in Fig. 1. The curves for the two groups are almost identical but at different levels. The systolic blood pressure of the normal subjects during exercise reaches a value which approximates the value for the hypertensive group at rest.

HEART RATES Heart rates both at rest and during exercise were higher in the hypertensive than in the normal subjects but the difference was not significant (Table VI). The rise during exercise was roughly the same in the two groups (Fig. 1).

VENOUS HEMATOCRIT The venous hematocrit was significantly higher ($p < 0.05$) in hypertensive than in normal subjects both at rest and during exercise. After exercise the hematocrit returned to resting values in the normotensive subjects. The hypertensive group still had high hematocrit values 6 minutes after the end of the work (Table VII and Fig. 2).

TOTAL PROTEIN VALUES The total protein values were slightly higher for the hypertensive than for the normotensive subjects at rest and during work (Table VIII and Fig. 2) but the difference was not significant. The hypertensive subjects but not

Table IV Anthropometric data

Subjects	Height (cm)	Weight (kg)	B.S.A. (M^2)
Normotensive			
\bar{x}	175.0	73.0	1.88
s	6.6	14.1	0.159
n	11	11	11
Hypertensive			
\bar{x}	165.5	81.1	1.90
s	9.1	25.2	0.10
n	14	14	14
p	> 0.05	> 0.05	> 0.05

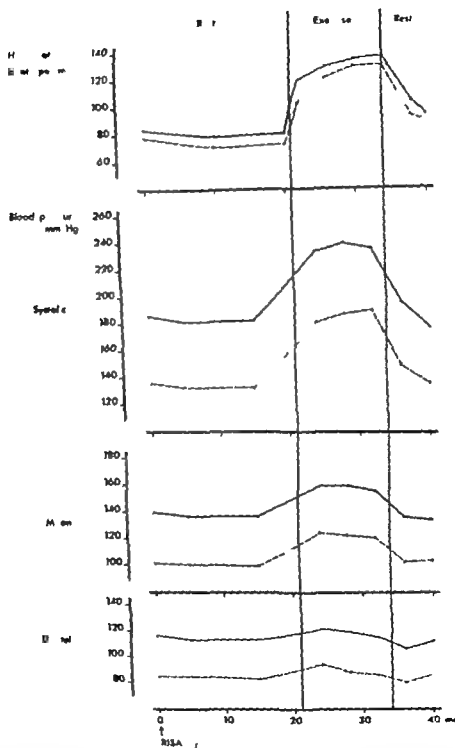


Fig. 1. Mean values for heart rate and blood pressure in normotensive subjects (dashed line) and hypertensive subjects (solid line). The mean pressure is calculated as the diastolic pressure plus one third of the pulse pressure.

Subjects	Rest			Exercise			Rest	
	0 min	5 min	15 min	24 min	5 min	52 min	36 min	40 min
Normotensive								
Systolic blood pressure								
\bar{x}	136	133	133	182	188	190	150	136
s	9	10	11	25	20	22	13	11
n	11	11	11	11	11	11	11	11
Mean blood pressure								
\bar{x}	102	101	100	123	123	121	101	101
s	7	8	7	7	7	8	7	8
n	11	11	11	11	11	11	11	11
Diastolic blood pressure								
\bar{x}	85	85	84	95	89	87	81	87
s	7	6	6	7	7	8	9	9
n	11	11	11	11	11	11	11	11
Hypertensive								
Systolic blood pressure								
\bar{x}	187	182	183	214	240	246	197	178
s	13	18	14	27	24	24	20	13
n	13	14	14	14	14	14	14	14
Mean blood pressure								
\bar{x}	140	137	137	160	160	156	137	135
s	9	8	7	9	10	10	7	9
n	13	14	14	14	14	14	14	14
Diastolic blood pressure								
\bar{x}	117	114	114	123	120	116	107	113
s	9	6	6	8	8	10	9	9
n	13	14	14	14	14	14	14	14

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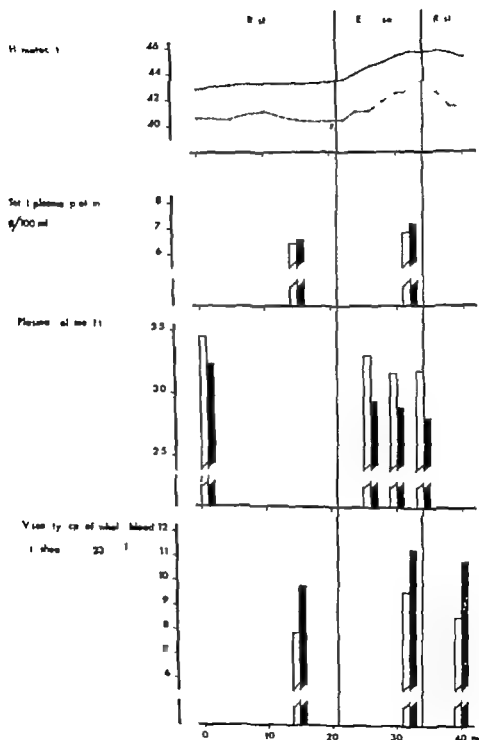


Fig 2 Hematocrit, total plasma protein, plasma volume and whole blood viscosity for both groups. Normotensive subjects indicated by dashed line or white bar. Hypertensive subjects indicated by solid line or black bar.

Table VII Hematocrit

Subjects	Rest		Exercise				Rest
	0 min	15 min	26 min	30 min	3 min	34 min	40 min
Normotensive							
\bar{x}	40.7	39.5	41.2	42.5	42.7	43.6	41.5
s	2.0	2.3	2.5	1.9	2.3	1.5	2.1
n	11	11	11	11	11	10	11
Hypertensive							
\bar{x}	42.9	41.3	41.6	43.4	43.7	43.7	43.3
s	1.9	1.9	1.8	3.2	2.4	2.7	2.7
n	14	14	14	14	14	14	14
p	<0.05	<0.01	<0.001	<0.01	<0.01	<0.05	<0.001

Table VIII Total serum proteins (Gm/100 ml)

Subjects	Rest (15 min)	Exercise (16 min)
Normotensive		
\bar{x}	6.43	6.86
s	0.58	0.44
n	11	11
Hypertensive		
\bar{x}	6.67	7.21
s	0.54	0.54
n	11	13
p	>0.05	>0.05

the normal subjects had a significant increase in their values from rest to exercise. There was no single fraction of plasma protein which was more responsible for the elevation than any other.

ABSOLUTE PLASMA VOLUME Absolute plasma volume was slightly lower for the hypertensive subjects at rest than for the normotensive subjects but the difference was not significant. During exercise the absolute plasma volume decreased both for normotensive and hypertensive subjects but the decrease was statistically significant only for the latter group. At

the end of exercise the absolute plasma volume was significantly lower in the hypertensive group than in the other group (Table IX and Fig. 2). When the plasma volume was expressed per kilogram of body weight the trend was clearer (Table X). From this it can be seen that there was a significantly decreased plasma volume at rest in the hypertensive group as compared to the normotensive. During exercise the plasma volume decreased significantly in both the hypertensive and the normotensive groups. The hypertensive group had a significantly decreased plasma volume per kilogram of body weight as compared to the normotensive group during exercise.

BLOOD VISCOSITY Tables XI and XII give data for the viscosity of whole blood and plasma for normotensive and hypertensive subjects at the shear rate of 23 inverse seconds. Fig. 3 gives mean values for whole blood viscosity at various shear rates (23, 46, 117 and 230 inverse seconds). The viscosity both of whole blood and plasma is higher at all rates of shear in hypertensive subjects than in normotensive subjects. The difference is statistically significant for whole blood but not for plasma. Whole blood viscosity increased at all rates of shear during work in both normal and hypertensive subjects ($p < 0.05$) and returned toward resting values after work ceased (Fig. 2). The viscosity

Table IX. Plasma volume (liters)

Subjects	Rest	Exercise		
		20 min	30 min	34 min
Normotensive				
x	3.46	3.31	3.17	3.19
s	0.51	0.57	0.47	0.49
n	11	11	11	11
Hypertensive				
x	3.24	2.90	2.85	2.71
s	0.35	0.37	0.35	0.38
n	14	14	14	14
p	>0.05	>0.05	>0.05	<0.05

Table X. Plasma volume (in ml/Kg of body weight) in the normotensive and hypertensive groups

Subjects	Rest	Exercise		
		20 min	30 min	34 min
Normotensive				
x	47.3	45.0	43.4	43.4
s	4.0	3.0	3.7	3.2
n	11	11	11	11
Hypertensive				
x	39.6	35.3	34.8	33.5
s	7.6	7.5	7.7	8.6
n	14	14	14	14
p	<0.005	<0.005	<0.005	<0.005

of plasma (Table XII) increased insignificantly during work in normotensive subjects and returned toward resting values after work ceased. For hypertensive subjects however the plasma viscosity decreased to below resting values after work ceased but this difference was not significant.

The hypertensive group included more obese subjects than the normotensive group but the difference in weight was

Table XI. Viscosity (centipoise) of whole blood at shear rate of 23 inverse seconds

Subjects	Rest (15 min)	Exercise (32 min)	Rest (40 min)
Normotensive			
x	7.86	9.37	8.43
s	1.02	1.99	0.95
n	11	11	11
Hypertensive			
x	9.86	11.31	10.90
s	0.98	1.50	1.11
n	14	14	13
p	<0.001	<0.05	<0.001

Table XII. Viscosity (centipoise) of plasma at shear rate of 23 inverse seconds

Subjects	Rest (15 min)	Exercise (32 min)	Rest (40 min)
Normotensive			
x	1.95	2.00	2.09
s	0.25	0.17	0.22
n	11	11	11
Hypertensive			
x	2.08	2.14	1.93
s	0.37	0.26	0.25
n	14	14	13
p	>0.05	>0.05	>0.05

not significantly different between the two groups.

In order to see whether these obese subjects could influence the results the one from the normotensive group and the five from the hypertensive group were excluded and the results were recalculated. There were still significant differences in hematocrit viscosity and plasma volume per kilogram of body weight at rest. The reactions of plasma volume, hematocrit viscosity, and total protein during exercise were unchanged in both the normotensive and hypertensive groups.

Table XII Hematocrit

Subjects	Rest		Exercise				R
	0 min	15 min	16 min	30 min	32 min	34 min	40 min
Normotensive							
\bar{x}	40.7	40.5	41.2	42.3	42.7	43.11	41.5
s	2.0	2.3	2.5	1.9	2.3	1.5	2.1
n	11	11	11	11	11	10	11
Hypertensive							
\bar{x}	42.9	43.3	44.6	45.4	45.7	45.7	45.5
s	1.9	1.9	1.8	2.2	2.4	2.7	2.1
n	14	14	14	14	14	14	14
p	<0.05	<0.01	<0.001	<0.01	<0.01	<0.05	<0.001

Table XIII Total serum proteins (Gm/100 ml)

Subject	Rest (15 min)	Exercise (32 min)
Normotensive		
\bar{x}	6.44	6.86
s	0.58	0.44
n	11	11
Hypertensive		
\bar{x}	7.62	7.21
s	0.54	0.51
n	13	13
p	>0.05	>0.05

the normal subjects had a significant increase in their values from rest to exercise. There was no single fraction of plasma protein which was more responsible for the elevation than any other.

ABSOLUTE PLASMA VOLUME. Absolute plasma volume was slightly lower for the hypertensive subjects at rest than for the normotensive subjects, but the difference was not significant. During exercise the absolute plasma volume decreased both for normotensive and hypertensive subjects, but the decrease was statistically significant only for the latter group. At

the end of exercise the absolute plasma volume was significantly lower in the hypertensive group than in the other group (Table IX and Fig. 2). When the plasma volume was expressed per kilogram of body weight the trend was clearer (Table X). From this it can be seen that there was a significantly decreased plasma volume at rest in the hypertensive group, as compared to the normotensive. During exercise the plasma volume decreased significantly in both the hypertensive and the normotensive groups. The hypertensive group had a significantly decreased plasma volume per kilogram of body weight as compared to the normotensive group during exercise.

BLOOD VISCOSITY. Tables XI and XII give data for the viscosity of whole blood and plasma for normotensive and hypertensive subjects at the shear rate of 23 inverse seconds. Fig. 3 gives mean values for whole blood viscosity at various shear rates (23, 46, 115 and 230 inverse seconds). The viscosity both of whole blood and plasma is higher at all rates of shear in hypertensive subjects than in normotensive subjects. The difference is statistically significant for whole blood but not for plasma. Whole blood viscosity increased at all rates of shear during work in both normal and hypertensive subjects ($p < 0.05$) and returned toward resting values after work ceased (Fig. 2). The viscosity

Table IX. Plasma volume (liters)

Subjects	Rest	Exercise		
		20 min	30 min	34 min
Normotensive				
\bar{x}	3.46	3.31	3.17	3.19
s	0.51	0.57	0.47	0.49
n	11	11	11	11
Hypertensive				
\bar{x}	3.24	2.90	2.85	2.71
s	0.35	0.37	0.35	0.38
n	14	14	14	14
p	> 0.05	> 0.05	> 0.05	< 0.05

Table X. Plasma volume (in ml/kg of body weight) in the normotensive and hypertensive groups

Subjects	Rest	Exercise		
		20 min	30 min	34 min
Normotensive				
\bar{x}	47.3	43.0	43.4	43.4
s	4.0	3.0	3.7	3.2
n	11	11	11	11
Hypertensive				
\bar{x}	39.6	35.3	34.8	33.5
s	7.6	7.5	7.7	8.6
n	14	14	14	14
p	< 0.005	< 0.005	< 0.005	< 0.005

of plasma (Table XII) increased insignificantly during work in normotensive subjects and returned toward resting values after work ceased. For hypertensive subjects however the plasma viscosity decreased to below resting values after work ceased but this difference was not significant.

The hypertensive group included more obese subjects than the normotensive group but the difference in weight was

Table XI. Viscosity (centipoise) of whole blood at shear rate of 23 inverse seconds

Subjects	Rest (15 min)	Exercise (37 min)	Rest (40 min)
Normotensive			
\bar{x}	7.86	9.57	8.43
s	1.07	1.99	0.95
n	11	11	11
Hypertensive			
\bar{x}	9.86	11.31	10.90
s	0.98	1.50	1.22
n	14	14	13
p	< 0.001	< 0.05	< 0.001

Table XII. Viscosity (centipoise) of plasma at shear rate of 23 inverse seconds

Subjects	Rest (15 min)	Exercise (3 min)	Rest (40 min)
Normotensive			
\bar{x}	1.95	2.00	2.09
s	0.25	0.17	0.22
n	11	11	11
Hypertensive			
\bar{x}	2.08	2.14	1.93
s	0.37	0.26	0.25
n	14	14	13
p	> 0.05	> 0.05	> 0.05

not significantly different between the two groups.

In order to see whether these obese subjects could influence the results the one from the normotensive group and the five from the hypertensive group were excluded and the results were recalculated. There were still significant differences in hematocrit, viscosity and plasma volume per kilogram of body weight at rest. The reactions of plasma volume, hematocrit, viscosity and total protein during exercise were unchanged in both the normotensive and hypertensive groups.

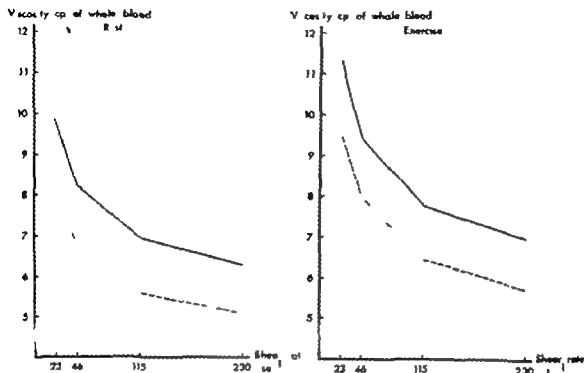


Fig. 3 Viscosity in centipoise of whole blood at rest and during exercise at different shear rates for normotensive (dashed line) and hypertensive (solid line) subject.

Discussion

It was found in a population study of men selected at random that the subjects with diastolic blood pressure ≥ 100 mm Hg had both increased hematocrit and total serum proteins even with the obesity factor eliminated. In the present study of two small representative samples from the total population examined an increased hematocrit, increased blood viscosity, and decreased plasma volume at rest per kilogram of body weight was found in the hypertensive group as compared with subjects with normal blood pressure. During physical exercise an increase in both hematocrit and whole blood viscosity and a decrease in plasma volume per kilogram of body weight was found in both groups where the plasma protein level increased only in the hypertensive group. The work load during exercise (600 k p m/min) was similar as indicated by the identical increases in heart rate in both groups. After work the values for plasma protein and viscosity returned toward resting values parallel with a decrease in blood pressure

and heart rate. In the hypertensive group however the hematocrit did not return to resting value during the period of observation.

In an evaluation of the results it is important to take into consideration the diurnal and seasonal variations in blood volume⁸ as well as the sex, age, and body build of the subjects. In our study all of these factors have been controlled with the exception of body build. It is well known that hypertensive individuals are more often overweight as was also the case in this study, but the difference was however not significant. Since the controls taken from the total normotensive population were of the same age and sex it would have been possible to match the controls with the hypertensive subjects and thus eliminate the obesity factor. It was considered however that since obesity itself exerts a significant influence on the cardiovascular system it must be regarded to be fundamentally a pathologic entity to which normal criteria do not apply. Therefore a random sample from a nor-

normotensive population was used instead of a matched group of obese normotensive subjects.

On the basis of our findings it is clear that obesity could not be responsible for the differences between the two groups. In the whole series from 1963 a higher hematocrit and greater total serum proteins were found in the group with diastolic blood pressure ≥ 100 mm Hg even when the obese subjects were excluded from the two groups.

The hematocrit levels in the present study are lower than in the 1963 study. The latter study was performed early in the morning whereas this study was done in the afternoon with the subjects in the recumbent position. In addition to this different hematocrit methods were used for the two examinations. However since we have not found any systematic differences between the two methods when used simultaneously it would appear that the time of day and the fact that in the latter study the subjects were recumbent can account for the differences in hematocrit.

Various findings have been reported for plasma volume in hypertensive subjects. Some reports present normal values^{2,12} with increased plasma volume having been found only in patients with congestive failure.⁶ Other observers have reported below normal values for circulating blood volume.^{11,13} Of interest is Glazer's finding³ in 1963 that there was a slight tendency to an elevated hematocrit in the early stages of hypertensive disease with a decrease evident in the later stages.

Our findings in the normotensive group are in agreement with those of Halperin and Weeseh,¹² which demonstrated that hemoglobin concentration, serum proteins and serum viscosity in normal subjects increased during work, and that plasma volume decreased. In their study resting values were reached within 25 minutes after moderate exercise but not after exhaustive work. The findings were similar in normal subjects and in patients with compensated heart disease. Lehinger and Buhmann¹ demonstrated a decreased plasma volume of 10 per cent in sitting work and 3.6 per cent in supine work. The erythrocyte volume was unchanged resulting in an increased hematocrit. The

decreased plasma volume is conceivably due to a movement of fluid into the extravascular space and most likely in the muscles which increase their volume during work.¹² Concerning the mechanism of the decrease in plasma volume the effect of vasopressor agents such as noradrenaline and angiotensin is of interest. These agents when injected in moderate pharmacologic doses result in a decreased plasma volume and an increased hematocrit and plasma protein level.¹ With withdrawal of these drugs resulted immediately in a drop in blood pressure below the control level and a rapid transcapillary refilling with increased plasma volume. The mechanism of this response is probably an increased movement of intravascular fluid into the extravascular space due to an increased resistance on the venular side of the capillary bed. It is not unlikely that the decreased plasma volume seen in normal and hypertensive subjects during work is due to such a phenomenon. Recently Eisenberg and Wolf¹⁴ published data on changes in plasma volume during quiet standing. They found a decrease of 13.2 per cent in a hypertensive group which was significantly greater than the 7.3 per cent decrease seen in the normal group. Mean arterial blood pressures rose in both groups.

Both the increased hematocrit and the increased plasma protein level must influence the viscosity of blood as demonstrated in this study. The hypertensive subjects usually have the type of blood pressure blood viscosity response at rest that is seen in normal subjects only during work. This is in agreement with the findings of Brod and associates⁵ who found an increased flow of blood in the muscles of hypertensive subjects and the suggestion that the hemodynamic pattern of these patients at rest resembles that of normal subjects during exercise.

Summary

Two groups of male subjects of the same age, one with early hypertensive disease and the other normotensive without heart disease, were studied before, during and after moderate exercise (600 k.p.m./min.). It was found that the hypertensive subjects at rest had significantly

higher hematocrit and whole blood viscosity, slightly higher plasma protein and slightly lower plasma volume than the normal subjects. During exercise a significant increase in hematocrit and whole blood viscosity was found in both groups. The plasma protein level increased and the plasma volume decreased significantly in the hypertensive group. It is suggested that there is an increased leakage of plasma water into the extravascular space in the hypertensive subjects with a decrease in plasma volume and increase in hematocrit viscosity and plasma protein level.

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Treatment of cardiac arrhythmias with beta-adrenergic blocking agents

Clinical and experimental studies

Sietem Wolfson M.D.

Samford I. Robbins B.A.

*Norman Krasnow M.D.**

Brooklyn N.Y.

Rapid progress has been made in the past decade in the treatment of cardiac arrhythmias. The introduction of electrical techniques for the conversion or control of many serious arrhythmias has gained rapid acceptance and wide spread use. Nevertheless arrhythmias which have not thus far proved to be amenable to electrical methods of control continue to pose difficult problems for the clinician. During this period few new pharmacologic approaches have proved to be useful.

Knowledge of the influence of catecholamines on the mechanical and electrical properties of the heart has been extended. However the relationship of catecholamines to clinical arrhythmias and in particular to arrhythmias provoked by digitalis therapy remains unclear. The introduction of effective means for blockade of beta adrenergic receptors provides an additional potent tool for study. Pronethalol was introduced by Black and Stephenson¹ in 1962 as an effective beta adrenergic blocking agent and Vaughan

Williams and Seluya² noted that this drug had an antiarrhythmic effect in guinea pigs. A subsequent analogue with similar properties propranolol was introduced in 1964.³

The purpose of the present study was to evaluate the effects of these two agents in the treatment of clinical and experimentally induced arrhythmias. These agents were shown to be useful drugs in specific circumstances. Like most therapeutic agents however they have toxic effects. This study describes several hazards of and contraindications to the administration of pronethalol or propranolol. Animal studies suggest a different mode of action than adrenergic blockade.

Materials and methods

Clinical studies Twenty-two patients with clinical arrhythmias were included in this series. There were 13 men and 9 women 30 to 88 years of age. In addition 5 subjects with normal sinus rhythm were studied. Arrhythmias were studied only if the mechanism was well defined and stable and its relationship to the adminis-

*From the Department of Medicine, Mt. Sinai University of New York Downtown Medical Center and the Medical Service, Mount Sinai Hospital, 100 East 17th Street, Brooklyn, N.Y.
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*Career Associate of the Health Research Council of the City of New York. Address: Department of Medicine, Mount Sinai University of New York Downtown Medical Center, 430 Chatham Ave., Brooklyn, N.Y. 11203

Table I *Clinical arrhythmias treated with pronethalol*

Patient	Sex	Age (yr)	Clinical diagnosis	Rhythm	Dose (mg)	Result
FL	M	59	Chronic bronchitis	Atrial premature contractions V R 150-180	50	Nodal rhythm V R 75
GH	F	80	Hypertensive heart disease CHF digitalis toxicity	NSR VPC (bigeminy) V R 80	50	NSR V R 60
AA	F	80	ASHD CHF digitalis toxicity	Atrial fibrillation VPC (bigeminy) V R 100	50	VPC abolished V R 80
IT	M	77	Emphysema CHF pericardium thorax	Atrial flutter 2:1 conduction V R 130	25	3:1 conduction V R 80
AS	F	88	ASHD CHF	VV dissociation with atrial captures atrial rate 95 V R 50	50	Captures disappeared atrial rate 80 V R 42
FA	F	61	RHD	Atrial flutter 2:1 conduction V R 110	50	Atrial flutter 4:1 conduction V R 70
JS	M	80	ASHD CHF digitalis toxicity	Sinus tachycardia wandering atrial pacemaker 1 AV block	50	NSR
IN	M	85	ASHD	Wandering atrial pacemaker VPC V R 80-120	100	No change
FM	M	30	Atrial septal defect pulmonary stenosis CHF	Atrial flutter 2:1 conduction V R 10	50	Carotid sinus massage increased block V R 75
JG	F	60	RHD mitral aortic regurgitation	Atrial fibrillation V R 160	50	Atrial fibrillation V R 100
FW	F	57	RHD mitral aortic regurgitation CHF digitalis toxicity	Atrial fibrillation VPC V R 100	50	Atrial fibrillation VPC abolished V R 80
EF	F	77	ASHD CHF	Atrial fibrillation VPC V R 140	50	VPC increased a number V R 170
LD	M	45	RHD mitral aortic regurgitation	Atrial fibrillation V R 140	50	Atrial fibrillation V R 80
BD	M	60	ASHD CHF	Atrial flutter 2:1 conduction V R 100	50	Atrial flutter 4:1 conduction V R 80
DG	M	60	ASHD CHF	Atrial flutter 2:1 conduction V R 130	100	Carotid sinus massage were of block V R 110
AV	M	46	RHD mitral aortic regurgitation CHF	Atrial fibrillation VPC V R 90	50	No effect
AC	M	57	RHD severe mitral regurgitation pulmonary hypertension CHF	Atrial tachycardia (177/min) nodal tachycardia VV dissociation V R 107	50	Complete heart block cardiac arrest
CR	M	41	Hyperthyroidism (controlled) myocarditis	NSR VPC V R 10	50	VPC abolished V R 60
JS	M	46	RHD M9 MI endocarditis (?) digitalis toxicity	Atrial tachycardia with 1:1 conduction (?) with carotid sinus pressure V R 125	50	Atrial focus altered to 104:1 conduction V R 104
JM	M	45	HCD chronic renal disease with arteriosclerotic disease	NSR incomplete VV dissociation (nodal rate 77) VPC (multifocal) V R 60	50	Complete VV dissociation (nodal rate 33 with increased atherotrombosis) VPC unchanged V R 60

Dose refers to dose of pronethalol (4 mg) in 12 hr maintenance

VPC = premature ventricular contraction

P = paroxysmal; S = sinus; T = tachycardia

RHD = Rheumatic heart disease; ASHD = Atherosclerotic heart disease; HCD = Hypertensive heart disease; CHF = Congestive heart failure; AV = Aortic valve; MV = Mitral valve; VPC = Ventricular premature contraction; NSR = Normal sinus rhythm; V R = Ventricular rate per minute

Table 1 Clinical arrhythmias treated with pronethalol—Cont d

Patient	Sex	Age (yr)	Clinical diagnosis	Rhythm	Dose (mg)	Results
RR	F	41	RHD (mild mitral insufficiency 2 yr after open mitral valvuloplasty) digitalis toxicity	Atrial fibrillation VPC VR 155	80	Atrial fibrillation no VPC VR 65
VF	F	48	ASHD acute myocardial infarction shock digitalis toxicity	NSR VPC (bigeminy) VR 120	30	Nodal rhythm VV dissociation VR 75

tration of digitalis clear. No patient with bronchospasm on auscultation was accepted. Congestive heart failure was not a contraindication for the purposes of this acute study.

The subjects were given either pronethalol* 30 mg or propranolol 5 mg intravenously over a 30 minute period. In 2 cases an additional 30 mg of pronethalol was given intravenously 20 minutes after the initial dose. Blood pressure was monitored by cuff frequently. Two patients (VV, RR) were given the drug only orally. Three patients were subsequently treated with oral pronethalol (300 mg three times daily) or propranolol (30 mg three times daily).

Animal studies. Twenty four studies were performed on 15 mongrel dogs approximately 15 kilograms in weight anesthetized with intravenous pentobarbital (20 mg per kilogram). A polyethylene catheter was introduced percutaneously into a peripheral vein. Electrocardiograms were monitored continuously. Ouabain (1.0 mg) was given intravenously and additional doses (0.25 mg) were repeated every 10 to 15 minutes until either ventricular tachycardia or multiple ventricular premature contractions were produced. The total dose of ouabain required for each animal averaged 65 mg per kilogram. When the toxic rhythm had been stabilized for at least 10 minutes pronethalol (mean dose

3 mg per kilogram) was given intravenously over several minutes. Electrocardiographic effects occurred within 20 minutes.

The animals were allowed to recover for several days from the procedure and then were given reserpine intraperitoneally 0.1 mg per kilogram daily for at least 2 or 3 days. This regimen has been shown to lower myocardial (atrial) catecholamines to 1 per cent of control levels.¹¹ Ouabain was again given according to the same schedule until toxicity developed. Pronethalol (mean dose 3.3 mg per kilogram) was then administered.

Ouabain alone was given to 7 animals until ventricular tachycardia developed and they were monitored without further treatment until death.

Clinical results (Table 1)

All patients who responded to pronethalol or propranolol did so within 15 minutes after completion of the infusion. One patient complained of nausea several minutes after treatment; this was relieved by an intramuscular injection of 200 mg of trimethoprim (Tigan, Roche). No other side effects were noted. The duration of effective blockade averaged 4 hours after intravenous administration and somewhat longer after oral administration.

The electrocardiographic changes that followed the administration of pronethalol can be divided into the effects produced upon the sinus node, the atria, the atrio-ventricular node and the ventricles. Since pronethalol was used in the majority of cases (see Table 1) the results will

*¹⁰ or ¹¹ or ¹² or ¹³ or ¹⁴ or ¹⁵ or ¹⁶ or ¹⁷ or ¹⁸ or ¹⁹ or ²⁰ or ²¹ or ²² or ²³ or ²⁴ or ²⁵ or ²⁶ or ²⁷ or ²⁸ or ²⁹ or ³⁰ or ³¹ or ³² or ³³ or ³⁴ or ³⁵ or ³⁶ or ³⁷ or ³⁸ or ³⁹ or ⁴⁰ or ⁴¹ or ⁴² or ⁴³ or ⁴⁴ or ⁴⁵ or ⁴⁶ or ⁴⁷ or ⁴⁸ or ⁴⁹ or ⁵⁰ or ⁵¹ or ⁵² or ⁵³ or ⁵⁴ or ⁵⁵ or ⁵⁶ or ⁵⁷ or ⁵⁸ or ⁵⁹ or ⁶⁰ or ⁶¹ or ⁶² or ⁶³ or ⁶⁴ or ⁶⁵ or ⁶⁶ or ⁶⁷ or ⁶⁸ or ⁶⁹ or ⁷⁰ or ⁷¹ or ⁷² or ⁷³ or ⁷⁴ or ⁷⁵ or ⁷⁶ or ⁷⁷ or ⁷⁸ or ⁷⁹ or ⁸⁰ or ⁸¹ or ⁸² or ⁸³ or ⁸⁴ or ⁸⁵ or ⁸⁶ or ⁸⁷ or ⁸⁸ or ⁸⁹ or ⁹⁰ or ⁹¹ or ⁹² or ⁹³ or ⁹⁴ or ⁹⁵ or ⁹⁶ or ⁹⁷ or ⁹⁸ or ⁹⁹ or ¹⁰⁰ or ¹⁰¹ or ¹⁰² or ¹⁰³ or ¹⁰⁴ or ¹⁰⁵ or ¹⁰⁶ or ¹⁰⁷ or ¹⁰⁸ or ¹⁰⁹ or ¹¹⁰ or ¹¹¹ or ¹¹² or ¹¹³ or ¹¹⁴ or ¹¹⁵ or ¹¹⁶ or ¹¹⁷ or ¹¹⁸ or ¹¹⁹ or ¹²⁰ or ¹²¹ or ¹²² or ¹²³ or ¹²⁴ or ¹²⁵ or ¹²⁶ or ¹²⁷ or ¹²⁸ or ¹²⁹ or ¹³⁰ or ¹³¹ or ¹³² or ¹³³ or ¹³⁴ or ¹³⁵ or ¹³⁶ or ¹³⁷ or ¹³⁸ or ¹³⁹ or ¹⁴⁰ or ¹⁴¹ or ¹⁴² or ¹⁴³ or ¹⁴⁴ or ¹⁴⁵ or ¹⁴⁶ or ¹⁴⁷ or ¹⁴⁸ or ¹⁴⁹ or ¹⁵⁰ or ¹⁵¹ or ¹⁵² or ¹⁵³ or ¹⁵⁴ or ¹⁵⁵ or ¹⁵⁶ or ¹⁵⁷ or ¹⁵⁸ or ¹⁵⁹ or ¹⁶⁰ or ¹⁶¹ or ¹⁶² or ¹⁶³ or ¹⁶⁴ or ¹⁶⁵ 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Table II Summary of the effects of pronethalol in clinical arrhythmias

Rhythm	Number of patients	Results (number of patients)
Sinus		
NSR	6	Slowed (5) Developed A V dissociation (1)
With A V dissociation	3	Slowed (3)
Atrial		
Extrasystoles	2	Abolished (2)
Flutter	5	No atrial effect (5)
Fibrillation	5	No atrial effect (5)
Ic by rdi	1	Atrial rate slowed (1)
A V node		
Atrial flutter	5	Ventricular rate slowed (5)
Atrial fibrillation	6	Ventricular rate slowed (6)
Dissociation	3	Increased block (3)
Tachycardia	1	Cardiac arrest (1)
Ventricular		
Extrasystoles		
Due to digitalis	6	Abolished in 5
Not due to digitalis	4	Abolished in 1

described in terms of this agent although the effects of propranolol were similar.

I Sinus rhythm. Of 8 patients with a sinus mechanism (Table II) the resting sinus rates slowed in 6 by 6 beats per minute. Five patients were exercised and had lesser increments in heart rate (10 beats per minute) after pronethalol. There was no change in the configuration of the P wave.

B Atrial arrhythmias. Two subjects had multiple atrial premature contractions with ventricular rates of 120 to 150 per minute. The premature beats were abolished by pronethalol in each case resulting in a stable nodal rhythm in one case and normal sinus rhythm in the other. The resultant ventricular rates averaged 80 per minute. In neither case was the arrhythmia thought to be related to digitalis toxicity.

Pronethalol had no effect upon the atrial mechanism in 10 patients with atrial flutter or atrial fibrillation (Fig. 1).

One patient (J.S.) with atrial tachycardia and 2:1 block due to digitalis had slowing of the ectopic atrial focus and ventricular rate but the 2:1 relationship persisted.

C Atrioventricular node. Pronethalol consistently produced a significant slowing of

the ventricular response in atrial fibrillation. Initial ventricular rates of 90 to 170 per minute were slowed to 60 to 90 per minute. In 4 patients of this group digitalis had failed to slow the ventricular rate despite clinical evidence of toxicity.

Pronethalol was also given to 5 patients with atrial flutter. Three patients responded with increased A V block and decreased ventricular rates. In 2 patients the ventricular rate slowed transiently during carotid sinus massage only after pronethalol. The above mentioned effects occurred despite the presence of congestive heart failure, severe anoxia (one case) and a spontaneous pneumothorax (one case).

Three patients with complete A V dissociation were treated. In 2 patients pronethalol slowed both the atrial and ventricular foci and ventricular captures disappeared (Fig. 2). The third subject with rheumatic mitral stenosis, very severe pulmonary hypertension and heart failure had a nodal tachycardia, a slower atrial tachycardia and A V dissociation (Fig. 3). In the attempt to abolish the ectopic tachycardia which was severely compromising cardiac output 30 mg. of pronethalol was given over 5 minutes. The patient

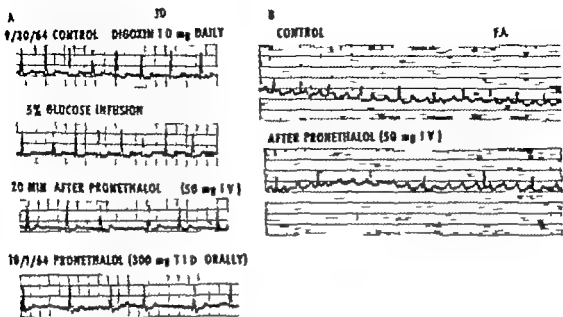


Fig 1 A Atrial fibrillation with rapid ventricular response despite digoxin 1.0 mg daily B Atrial fibrillation with rapid response In each case pronethalol slows the ventricular rate without effect on the atrial mechanism

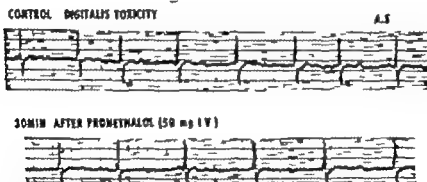


Fig 2 AV dissociation secondary to digitalis intoxication Pronethalol slowed the atrial rate from 91 to 60 per minute the ventricular rate from 50 to 47 per minute and abolished ventricular captures (C)

developed complete heart block with an idioventricular rhythm as the infusion was completed and within 2 minutes cardiac arrest supervened. Rapid intravenous administration of isoproterenol and intracardiac epinephrine as well as the usual resuscitative measures were unable to reverse the arrest.

Effect on ventricular effects No changes in QRS configuration or duration were noted. Pronethalol was successful in 5 of 6 patients in abolishing ventricular extrasystoles which were considered to be due

to digitalis toxicity (Fig 4) but one of these subjects developed AV dissociation. Of 4 patients with frequent ventricular premature beats unrelated to digitalis one responded to pronethalol. One of the refractory patients (EF) presented with atrial fibrillation a rapid ventricular response and frequent ventricular ectopic beats. She had received 1.6 mg of lanatoside C. Pronethalol slowed the ventricular rate but the extrasystoles increased in frequency. She was then treated with additional lanatoside C with further slowing

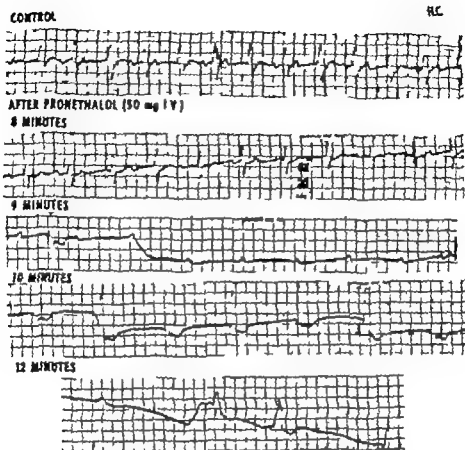


Fig. 3. A dissociation with sinus and nodal tachycardia in a patient with chronic stenosis and severe polymorphic hypertension. Cardiac arrest followed progressive slowing of the nodal sinus and ventricular pacemakers.

of the ventricular rate and abolition of the extrasystoles.

Animal studies (Table III)

Eight dogs had 11 episodes of ouabain-induced ventricular arrhythmia treated with pronethalol. In 7 of these episodes pronethalol caused reversion to a supraventricular tachycardia.

When 6 of these animals had been pretreated with reserpine they also developed ventricular tachycardia after ouabain. All 6 episodes of ventricular tachycardia were successfully converted to a supraventricular mechanism (although in 2 cases the result was only transient) (Fig. 5). In this small group of animals there was no increase in the toxic dose of ouabain after reserpine.

None of the animals succumbed to ouabain toxicity when pronethalol was

given even when the ventricular arrhythmia did not revert to a sinus mechanism during the 3 hour period of observation. By contrast 7 animals were given ouabain until toxicity developed but pronethalol was withheld. All died of arrhythmia either ventricular standstill or fibrillation.

Discussion

Sympathomimetic agents have found wide clinical application both for their potentiation of cardiac contractility and their stimulatory effect on pacemaker sites.⁶ Adrenergic stimulation of the heart produces^{7,8} increased rhythmicity of the sinus node, a shortened refractory period in atrial muscle, more rapid atrioventricular conduction and enhanced activity of idioventricular pacemakers. These effects are thought to be subserved by beta adrenergic receptors within the heart.^{9,10}

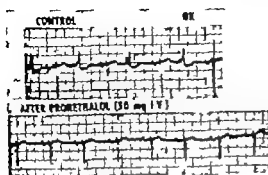


Fig. 4. Reversal of ventricular bigeminy due to digitalis toxicity. Note also slowing of sinus rate.

Hoffman² suggests that the increased rate of diastolic depolarization of pacemaker cell membranes is the cellular basis for increased rhythmicity and automaticity. He considers that all pacemaker sites defined as automatic cells are located within the conduction system. Wallace and Sarnoff¹ have shown that conduction in Purkinje tissue and ventricular myocardium is not significantly affected by sympathetic nerve stimulation.

Given this broad spectrum of activity, it might prove to be valuable in certain circumstances to minimize sympathetic influences upon the heart. Until recent years, however, selective beta adrenergic blockade has not been possible. The dichloro derivative of isoproterenol offered

promise in this direction but further experience showed that it has a significant intrinsic sympathomimetic effect.¹² In 1962, pronethalol, the naphthyl derivative of isoproterenol, was introduced¹ and proved to be an effective antagonist of the beta adrenergic catecholamines. It prevented the chronotropic and motropic effects of intravenous isoproterenol and stellate ganglion stimulation in both animals and man.^{1,12} In addition, it produced a bradycardia in acutely sympathectomized animals and thus is thought to be effective against myocardial stores of catecholamines. However, 11 per cent of rats given pronethalol in high doses for prolonged periods of time developed lymphosarcomas. Propranolol, a noncarcinogenic analogue with pharmacologic properties similar to pronethalol, has now replaced pronethalol.¹

Arrhythmias

Evidence has been presented which suggests that pronethalol may be a potent antiarrhythmic agent. The data demonstrate effects of beta adrenergic blockade at several levels of the pacemaker and conduction system of the heart.

The 3 patients with normal sinus rhythm showed slowing of cardiac rate both at rest and exercise rates. This result is consistent with reported studies utilizing both pronethalol and catecholamine-depleting agents in animal and human subjects.^{1,12,13} One patient with complete A-V

Table III. Reversal of enoxacin-induced ventricular tachycardia in the dog by pronethalol before and after reserpine pretreatment.

Number of dogs	Quinidine mean dose (mg)	Arrhythmia	Pronethalol mean dose (range) (mg)	Result
Without reserpine 11	1.2	Ventricular tachycardia	110 (25-180)	Supra-ventricular tachycardia 7† Ventricular tachycardia 4
With reserpine pretreatment 6	1.2	Ventricular tachycardia	65 (7.5-160)	Supra-ventricular tachycardia 4 Ventricular tachycardia 0

1 mg = 0.1 ml in 10% aqueous solution. Dose (1-60) of propranolol.
†Transients in 2.

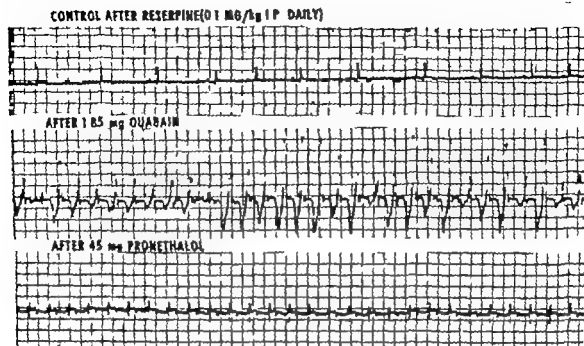


Fig. 5. Ouabain induced ventricular tachycardia in the reserpined dog. Pronethalol caused reversion to a sinus mechanism.

demonstration had slowing of both the sinus and ventricular rates as did dogs with surgical heart block treated with reserpine by Roberts and Modell.¹⁹

There was no change in the atrial rate of atrial flutter consistent with reports of others.^{11,12} Atrial premature contractions, however, have been decreased in number. Reversal of paroxysmal atrial tachycardia with block caused by digitalis toxicity has been reported¹⁴ although in the present case only slowing of the ectopic focus was achieved.

Pronethalol consistently slowed conduction across the AV node as evidenced by slowing of the ventricular rate in atrial flutter and fibrillation and development of AV dissociation. This effect is consistent with the results of experimental studies. Conduction through the AV node is increased by sympathetic nerve stimulation^{11,12} and decreased in acute or chronic sympathectomy or treatment with reserpine.²⁰ Reserpine has also been shown to increase AV block in patients with atrial fibrillation.¹

The results thus far suggest that pronethalol may inhibit ventricular extrasystoles

particularly when caused by digitalis toxicity. This has been shown by others.^{11,12,13} Adrenergic blockade by other means can also prevent or reverse ventricular irritability related to digitalis toxicity,^{14,15} but the fundamental relationship between digitalis and catecholamines is unclear. Tinz^{16,17} reported abolition of the positive inotropic effect of ouabain upon cat papillary muscles when the strips were pretreated with dichloroisoproterenol, reserpine, or guanethidine. Other workers using diverse means of inhibiting catecholamine activity have found that pronethalol + reserpine²¹, acute or chronic sympathectomy, total cardiac denervation²² or ATVI 10¹ do not inhibit the positive inotropic action of digitalis preparations.

The present studies in animals indicate that the ventricular irritability caused by digitalis is not solely related to adrenergic stimuli since the dogs pretreated with reserpine also developed ventricular ectopic rhythms in response to ouabain. Similarly, digitalis toxicity may be observed in the totally denervated heart²² or the reserpined cat papillary muscle.²¹

Moreover the present data show that pronethalol reverses ouabain induced ventricular tachycardia even in reserpine pretreated dogs¹ suggesting a mechanism of action other than beta blockade.* Lucchen⁷ and Somani and Lum²¹ also concluded from time dose relationships and the effects on action potentials that pronethalol has a nonspecific action which may be responsible for its antiarrhythmic effect.

Clinical indications and contraindications

The indications for the use of pronethalol in cardiac arrhythmias appear thus far to be limited but specific. The most useful effect has been the slowing of the ventricular rate in atrial fibrillation or flutter when this was not otherwise possible by large or toxic doses of digitalis. It also produces a rapid and relatively prolonged reversal of increased ventricular irritability especially when caused by digitalis. This may be particularly useful when the administration of potassium is not effective or is contraindicated. Unlike calcium verenate pronethalol need not be infused repeatedly. On the other hand the underlying congestive failure for which digitalis was prescribed may be aggravated by the prolonged use of the adrenergic blockade.

The only death reported due to pronethalol occurred in the present series although we are aware of several others²² two instances in subjects with congenital heart disease.²³

Pronethalol is contraindicated in the presence of bradycardia since the rates of all pacemaker sites are lowered by the drug. Complete A-V dissociation or a high degree of A-V block would also appear to preclude the use of pronethalol since the higher pacemakers may be suppressed along with the lower ones. The hazard is analogous to the use of quinidine in this situation.

No signs of increased pulmonary con-

gestion were encountered in this study in 14 patients with congestive heart failure treated with a single intravenous dose of pronethalol. Although the cardiac output of normal subjects is not decreased after guanethidine²⁴ reserpine²⁷ sympathetomy²⁷ or pronethalol^{1, 22, 28} subjects with congestive heart failure may be dependent upon a catecholamine stimulus for adequate myocardial function and thus may react to long term administration of pronethalol with a worsening of their congestive heart failure.^{16, 24, 29} Until additional data are available therefore the presence of moderate to severe congestive heart failure should be considered to be a relative contraindication to the chronic administration of pronethalol. Perhaps an exception would be the case in which a rapid ventricular rate is contributing to the failure.

Beta adrenergic blockade may cause a fall in venous return since it has been shown that beta receptors in the peripheral venous bed subserve venoconstriction.³⁰ This suggests that pronethalol should be used with caution in conditions such as pulmonary hypertension and congestive heart failure in which an adequate venous return is essential for maintaining cardiac output.

In addition the drug blocks the bronchodilator effects of the catecholamines and its use should be avoided when bronchospasm is present.

Finally a potential hazard exists in stenosis of the semilunar valves since experimentally catecholamines may be required to maintain adequate velocity or force of ventricular contraction.³¹

Summary

Twenty seven subjects with various cardiac rhythms were treated with intravenous pronethalol or propranolol. Slowed sinus rhythmicity decreased A-V node conduction and decreased ventricular premature contractions (particularly if caused by digitalis) were observed. One death occurred in a patient with A-V dissociation, severe pulmonary hypertension and congestive heart failure. No other significant side effects were seen.

These two drugs are considered to be quite useful in controlling ventricular responses to atrial flutter or fibrillation.

*It is possible that small residual stores of catecholamines not removed by reserpine (presumably 2 per cent)²⁴ might cause an effect we trigger for digitalis-induced arrhythmias. In the future it is difficult to avoid the possibility that pronethalol may produce its effect by beta blockade alone.

and in certain cases of ventricular irritability. They are rapid acting, and potent. Their use may be hazardous when bradycardia or A-V dissociation is present or if the arrhythmia is complicated by severe congestive heart failure or bronchospastic pulmonary disease.

Data in animals confirm the reversal of digitalis toxicity and suggest a mechanism of action in addition to beta adrenergic blockade.

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A pathologic-arteriographic correlation of renal arterial disease

*Lawrence J. McCormack, M.D.**

*Engene F. Poulasse, M.D.***

Thomas F. Meaney, M.D.

*Thomas J. Hoto, Jr., M.D.****

Harriet P. Duxon, M.D.

Cleveland, Ohio

Various types of lesions produce renal arterial stenosis. Although atherosclerosis is the most common, there are other lesions that are being recognized with increasing frequency. Our early experience suggested that most disease that was not atherosclerotic represented fibromuscular hyperplasia¹ following the original report; other types were identified and now we know that fibromuscular hyperplasia occurs less frequently than types with dominance of fibrosis and absence of muscular hyperplasia. Further, more continuing experience has shown that these renal arterial diseases may have distinctive arteriographic features that in themselves can be diagnostic when the length of renal artery affected is sufficient for the entire pattern to be displayed.

This report describes the pathologic and arteriographic characteristics of renal arterial lesions in 97 patients, most of whom were examined before 1963. On the basis of microscopic features, the

lesions were classified according to their primary locations in the vessel walls. There were two types of lesions primarily of the intima: atherosclerosis and intimal fibroplasia; and three types predominantly affecting the media: medial fibroplasia with aneurysm, fibromuscular hyperplasia, and subintimal fibroplasia. Only patients who had total arterial resections were included.

Materials and methods

Arterial segments were obtained at the time of operation in 94 patients who were operated upon for relief of diastolic hypertension and at autopsy in the other 3. After the specimens were treated by the standard fixing procedures, either a modified Zenker's or formalin, appropriate sections were obtained depending on the nature of the lesion. When long segments of an artery were affected, longitudinal sections often provided the clearest picture of the pathologic features. When an artery

*Fellow in the Division of Pathology, the Department of Urology, the Division of Radiology, and the Division of Research, The Cleveland Clinic Foundation, Cleveland, Ohio.

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Address: Division of Pathology, The Cleveland Clinic, 3636 East 93rd St., Cleveland, Ohio 44106.

any correspondence with the staff Department of Urology, P. O. Box 46, 3804 Madison Ave., Cleveland, Ohio.

***Formerly, Special Fellow in Cardiology, P. O. Box 46, 3804 Madison Ave., Cleveland, Ohio.

was completely occluded cross sections permitted ready recognition of the site of the original lumen. Sections were stained with the usual hematoxylin and eosin stains and for connective tissue with Mallory Hendenham, Masson trichrome, Verhoeff Van Gieson, Gomori elastic and toluidine blue and Rinehart Abul Hay stains. Sudan IV was used on selected frozen sections from unprocessed blocks.

Renal arteriography had been performed in each patient about three fourths of the arteriograms had been obtained by trans lumbar aortic injection of contrast medium² and the rest by selective renal arterial injection.⁴

Results

The number of patients in each diagnostic group as well as the age and sex distributions are shown in Table I.

Atherosclerosis was present in 30 patients, 23 men and 7 women ranging in age from 28 to 68 years. Two types of lesions were found. In about one third of the cases there was a circumferential atheroma with areas of accumulation of lipid and often focal calcification (Fig. 1). In the larger group the intima was thickened by an eccentric fibrous plaque often composed primarily of collagen. However Sudan IV staining of frozen sections showed some deposition of lipid permitting the designation of the lesion as an old atheroma. With both types of lesions two complicating features were sometimes found—thrombosis and dissecting hema-

toma originating distal to the point of maximal narrowing. Both types usually produced complete arterial occlusion.

Renal arteriography showed these lesions to be predominantly in the first 2 cm of the renal artery (Fig. 2). Bilateral disease occurred in 12 of the 30 patients. The stenosis often appeared to be asymmetrical reflecting the gross and microscopic findings of localized formation of plaques. Poststenotic dilatation was frequent. In some patients complete occlusion had occurred because of either thrombosis or hematoma and only a short stub of renal artery was clearly visible (Fig. 3).

Intimal fibroplasia occurred in 14 patients, 9 males and 5 females whose ages ranged from 18 months to 48 years. Microscopically this fibroplasia was found to be a lesion of the intima and *elastica interna*. The intimal hyperplasia appeared as a segmental circumferential accumulation of cellular collagen without a lipid component (Fig. 4). The collagen was somewhat primitive at times it stained metachromatically with toluidine blue and positively with colloidal iron. There are possibly two types of this lesion because that found in youthful patients seemed to be different from that in the adults. In the former the *elastica interna* was often reduplicated and there was slight disorganization of the media in contrast in the adult variety these aberrations were not present. In some specimens the collagen was closely applied to large folds of the *elastica* as though arterial spasm had

Table I. Age and sex distributions in renal arterial diseases in 97 patients

Site and type of lesion	Total number	Males		Females	
		Number	Age range (yr)	Number	Age range (yr)
Intima					
Atherosclerosis	20	23	8-68	7	45-65
Intimal fibroplasia	14	9	15-41	5	33-48
Media					
Medial fibroplasia	15	3	41-58	12	30-59
Fibromuscular dysplasia	1	5	15-40	2	10-17
Subintimal fibroplasia	21	5	17-40	16	14-48
Grand total	97				

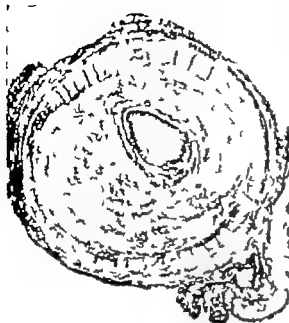


Fig 7 A severe degree of concentric atherosclerosis complicated by thrombosis in pre-ent iliofemoral vein and down take magnification $\times 12$

occurred and the artery had been fixed in that state by the accumulation of collagen. Often a segment of the internal elastic membrane distal to the stenosis had completely disappeared resulting in either of two types of aneurysms. One a dissecting aneurysm (intramural hematoma) occurred proximal as well as distal to the stenosis and in the proximal extension overrode the area of stenosis (Fig 5). The other was an aneurysmal dilatation due to destruction of almost the entire vessel wall and only the adventitia provided continuity (Fig 6).

The arteriographic features seemed to depend on the integrity of the internal elastic membrane. When the *elastica* was intact fibroplasia produced a symmetrical narrowing of the main renal artery or the primary branches with poststenotic dilatation (Fig 7). When it was disrupted the resultant aneurysm appeared as a dilated segment (Fig 8). Sometimes the stenosis was not apparent because of proximal dissection and the only arteriographic abnormality was an irregularly dilated artery. It was the irregularity that distinguished this dilatation from the poststenotic type. The dissecting aneurysm



Fig 8 Selective renal arteriogram showing asymmetrical narrowing by an atherosclerotic plaque in the first portion of the artery with poststenotic dilatation. Presence of this plaque was confirmed at operation when an endarterectomy was performed.



Fig 9 Trans-lumbar aortogram and renal arteriogram in a patient with atherosclerosis in the first portion of each renal artery. On the right there is slight irregularity in the outline of the vessel. On the left the arterial outline is abruptly probably because of complete or nearly complete occlusion had been produced by the thrombosis that was found in the segment removed at the time of nephrectomy. The faint arterial filling distally suggests either that this artery was not completely occluded by the thrombus or that collateral circulation was adequate to produce faint opacification.

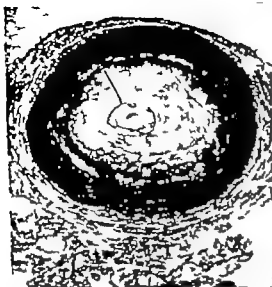


Fig. 4 Intimal fibroplasia in an infant. Photomicrograph of cross section of renal artery close to aorta. The subintimal collagenous zone (arrow) superimposed on the internal elastic membrane is extensive. The elastic fibers seen in the media in this section occur normally in the first portion of the renal artery as an extension of the medial elastic fibers of the aorta. Verhoeff/Van Gieson stain, magnification $\times 55$.



Fig. 6 A photomicrograph of a renal artery distal to a stenosis produced by intimal fibroplasia. There is almost complete destruction of the arterial wall (top) and only the external elastic membrane is intact. Intimal fibroplasia is seen superimposed on remnants of the internal elastic membrane (right hand and lower portions of the section). Verhoeff/Van Gieson stain, magnification $\times 36$.



Fig. 5 Intimal fibroplasia in a polar branch of the renal artery. The large channel is part of a dissecting hematoma. Verhoeff/Van Gieson stain, magnification $\times 18$.



Fig. 7 Translumbar arteriogram of intimal fibroplasia of the superior branch of the left renal artery. The arrow indicates poststenotic dilatation of secondary branches. The stenosis is just proximal to the renal hilum. The large artery dilated in the renal portion of the kidney. At operation the upper pole of the kidney was removed. On macroscopic examination the internal elastic membrane of the arterial branch was intact.



Fig. 8 Translumbar renal arteriogram of intimal fibroplasia of the left renal artery with disrupted internal elastic membrane and aneurysmal poststenotic dilatation. There are two and perhaps three areas of aneurysmal dilatation the proximal one overlies and obscures the stenosis.



Fig. 9 Photograph of longitudinal bisection of renal artery showing corrugations and orifices of aneurysms in medial fibroplasia.

could not be differentiated from aneurysmal dilatation and appeared only as an irregularly dilated segment.

Medial fibroplasia with aneurysms is the lesion that produces the string of beads arteriogram usually considered to be characteristic of fibromuscular hyperplasia.⁶ It was present in 15 patients: 12 women who ranged in age from 30 to 39 years and 3 men who were 41 to 58 years of age. Grossly the artery was irregularly dilated the dilatations on longitudinal sections representing aneurysmal outpouchings (Fig. 9). Microscopically the lesion was often seen in long segments of the renal



Fig. 10 Longitudinal section of medial fibroplasia showing severity and variability of destruction of arterial wall. Verhoeff-Van Gieson stain magnification $\times 20$.

artery and sometimes in the primary branches. In some areas there was destruction of the intima *elastica interna* and the media producing aneurysms. These areas alternated with segments of media in which the smooth muscle and fine elastic digitations were lost and replaced by collagen (Fig. 10) much as can be seen in aging muscular arteries. Intimal fibroplasia was sometimes present in areas in which the vessel wall was still intact and seemed to be capable of producing stenosis.

On arteriograms the lesions often were bilateral usually the first centimeter of the renal artery was spared but in some cases the entire length distal to that including the primary branches was affected. The beading was produced by aneurysmal segments (the beads) joined by short segments which sometimes did not appear to be narrowed (Fig. 11). The characteristic feature of the beads was the aneurysmal nature since almost without exception their diameters exceeded that of the apparently unaffected proximal



Fig. 11 Selective right renal arteriogram of medial fibroplasia. The arrow indicates the apparent proximal and distal limits of the disease. The characteristic feature is the aneurysmal dilatation which is wider than the apparently unaffected proximal artery (cf. arteriogram of subadventitial fibroplasia).



Fig. 12 Snout-of-head arteriogram of medial fibroplasia of the left renal artery (between the arrows). Regions of stenosis are apparent and these separate areas of aneurysmal dilatation which are of greater diameter than the seemingly unaffected proximal artery.

artery (Fig. 12). In most patients short segments of stenosis were present however the aneurysmal beading permitted a correct anatomic diagnosis to be made from the arteriograms. This retrospective study did not permit a comparison of stenotic areas seen on arteriograms with the presence of intimal fibroplasia and it may be that even in a prospective study such a comparison would not be feasible.

Fibromuscular hyperplasia was present in only 7 patients. Three of these 1 boy and 2 girls ranged in age from 10 to 17 years; the other 4 were men from 29 to 45 years of age. In the younger patients the hyperplasia occurred as a segmental concentric stenosing lesion composed of an unorganized mixture of smooth muscle and fibrous tissue. The quantities of the two components were variable in the case originally described¹⁴ the two seemed to be equal in amount (Fig. 13) but in the 2 later cases muscular tissue predominated. In the 4 men an additional feature was disruption of the *elastic interna* distal to the stenosis with formation of a dissecting aneurysm.

The arteriographic findings indicated either stenosis or aneurysm. In the 3 young patients the internal elastic membrane



Fig. 13 Cross section of fibromuscular hyperplasia showing medial thickening because of increased amount of fibrous and muscle tissue. The internal elastic membrane is absent. Verboef Van Geenen stain magnification $\times 100$.



Fig. 14 Arteriogram showing severe stenosis of the orifices of both renal arteries produced by fibromuscular hyperplasia. Characteristically symmetrical poststenotic dilatation is seen on the left as well as coarctation of the abdominal aorta. The large inferior mesenteric artery may have been furnishing collateral blood supply to the left kidney.

was intact and the arteriogram showed a symmetrical stenosis with poststenotic dilatation. In 1 of these the lesion occurred in a large primary branch just beyond its origin. In 2 stenoses of the orifice of the main renal artery were present, one bilateral (Fig. 14) and the other unilateral. In these 3 patients there was narrowing (coarctation) of the abdominal aorta which extended from above the origin of the renal arteries to or close to the aortic bifurcation. In the 4 older patients dissection had occurred which obscured the stenosis. In each of 3 the artery was irregularly dilated and the dilatation was indistinguishable from that found in intimal fibroplasia. In 1 the translumbar arteriogram appeared to be normal but at operation the posterior branch was found to be completely obstructed by a dissecting aneurysm containing a thrombus. Clearly an oblique arteriogram would have permitted preoperative recognition of the occlusion of the arterial branch because in the nephrogram phase of the arteriogram the posterior segment would not have been opacified.

Subadventitial fibroplasia was present in 31 patients: 5 males and 26 females ranging in age from 14 to 28 years. The lesion was made up of dense collagen enveloping

the renal artery for varying lengths up to as much as 2 cm. This collagenous material was in the outer portion of media (Fig. 15) often replacing it irregularly and causing much disorganization of the muscular coat. Islands of smooth muscle cells were entrapped in the dense fibrotic tissue. The *elastica interna* was intact and occasionally segments of intimal fibroplasia were present but these were insignificant compared to the amount of peripheral fibrosis. Special staining techniques highlighted the changes and showed that the external elastic membrane was also affected and that the lesion therefore was not completely subadventitial in location (Fig. 16).

Arteriography showed subadventitial fibroplasia to be a severely stenosing lesion primarily of the right renal artery. The right side was affected in 18 patients, the left side in 7 and both sides in 6. The length of artery involved varied from a sharply localized area (Fig. 17) to the distal two thirds of the main trunk. Branches often were affected. Disease of the main renal artery was found in 27

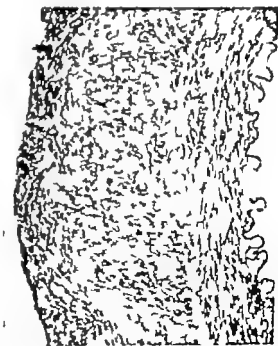


Fig. 15 Photomicrograph of subadventitial fibroplasia showing the presence of a dense sclerotic band between remnants of media and adventitia. Hematoxylin-eosin stain, magnification $\times 80$.



Fig. 16 Photomicrograph of a cross section of subadventitial fibroplasia showing dense collagen replacing most of the external elastic membrane and the media. The thickness of the collagen is indicated by the arrow. Verhoeff Van Gieson stain; magnification $\times 60$.



Fig. 17 Right renal arteriogram showing a sharply localized stenosis (arrow) of the lower right renal artery produced by subadventitial fibroplasia.



Fig. 18 Subadventitial fibroplasia of the right renal artery (between arrows). The stenosis is severe and accompanied by prominent collateral blood supply. Characteristically the stenosis is arched giving the impression of beading; however the beads are not aneurysmal (cf medial fibroplasia Figs 11 and 12).

patients and in 13 of these it extended into the branches also. Lesions of the branches without involvement of the main trunk occurred in 2 patients. As for the other 2 patients each had two renal arteries supplying the right kidney, one artery was normal and the other stenotic.

Within the affected segments of main arteries the stenosis was variably severe with regions of intense narrowing alternating with those of lesser stenosis (Fig. 19). This gave the appearance of beading. This beading was not aneurysmal as in medial fibroplasia because the width of the beads was less than that of the unaffected proximal artery. Collateral blood channels bypassing the stenosis occurred frequently perhaps indicating the severity of stenosis.

Discussion

Understanding of the pathology of renal arterial diseases has been greatly aided by using a combination of tissue fixing and sectioning techniques to obtain a three dimensional concept of each type of lesion. When sequential cross sections are used,

as in the study of aneurysms associated with intimal fibroplasia or fibromuscular hyperplasia it is best to fix the entire arterial segment before cutting the sections. Longitudinal sections are helpful in examining medial fibroplasia and to obtain these the fresh arterial segment should be opened longitudinally before careful fix fixation. After fixation parallel sections can be easily cut. This type of fixation and sectioning should not be used for examination of the occluded artery because in this situation it does not permit ready identification of the original anatomic landmarks. Important information can often be obtained from study both of cross sections and of longitudinal sections of different parts of the same artery.

Our first reports⁶ of the pathology of renal arterial disease described findings in a small number of arteries. With more experience it became apparent that the original designation of nonatherosclerotic lesions as fibromuscular hyperplasia and segmental mural fibrosis did not adequately describe the variety of changes observed. The present classification takes these varieties into consideration and is accordingly based on the predominant microscopic features and their primary locations in the vessel walls. This classification is similar to that described by Hunt and associates⁷ with the advantage that a rather close pathologic arteriographic correlation is possible.

During the years of growing interest in renal arterial disease diagnosis of atherosclerotic stenosis did not present a problem. The gross and microscopic pathology was readily recognized and the location of stenotic lesions predominantly at the orifice permitted arteriographic diagnosis even before techniques were available for visualizing the entire renal arterial supply.⁸⁻¹⁰ Continuing experience has shown that these lesions occur more frequently in men than in women and at the time of life when symptoms of atherosclerosis appear. The plaque is almost always at the orifice or in the first 2 cm of the renal artery. It usually produces an asymmetrical stenosis that often is accompanied by poststenotic dilatation. For preoperative diagnosis knowledge of the patient's age and sex as well as the site and arteriographic ap-

pearance of the lesion permits a high degree of accuracy.

Recognition of the various types of renal arterial disease that are not atherosclerotic has evolved slowly. The first report seems to be that of Jendbetter and Burkhead¹¹ in 1938 which described a cure of hypertension by nephrectomy in a 5-year-old boy. The excised renal artery had been obstructed by a scum of mass of muscular tissue covered by normal appearing intimal elastic membrane and intima. The arterial wall itself seemed to be normal except at the origin of the mass.

Development of renal arteriography in the nineteen fifties increased interest in occlusive renal arterial disease. Some early reports described fibrous lesions, one lesion was found in the outer media¹² and the rest were considered to be located in the intima.¹³⁻¹⁵ One case at our institution¹⁶ was later reclassified as fibromuscular hyperplasia.¹⁷ In 1958 Johnston by McCormack, Hurst and Loutch¹⁸ divided the nonatherosclerotic lesions into fibromuscular hyperplasia and segmental mural scarring (the latter is now called subintimal fibroplasia). Later Wyke and associates^{17,19} and Wellington¹⁹ used the term fibromuscular hyperplasia to include all types of lesions that are not atherosclerotic.

The results of the study reported here indicate that fibroplasia is the dominant feature of most fibrous disease and that muscular hyperplasia is unusual. Although we reserve the term *fibromuscular hyperplasia* for the uncommon lesions with increased amounts of both fibrous and muscular tissue the term *fibroplasia* seems to be a better description for most of the lesions that are not atherosclerotic. Furthermore the designation of the primary site of the fibroplasia (i.e. intimal medial subintimal or ventricle) is helpful because of associated anatomic and clinical features. This classification of nonatherosclerotic renal arterial disease although useful diagnostically gives no indication of etiological factors.

The youthful type of intimal fibroplasia can affect not only the renal arteries but also the adjacent aorta and orifices of splenic, celiac and hepatic arteries.¹⁴ Brust and associates¹⁴ have pointed out that aortic involvement can produce long segments of abdominal coarctation. In our

experience this has not caused arterial pressure gradients large enough to suggest a clinical diagnosis of aortic coarctation. The relationship between the changes in various age groups is not clear but it is the dissolution of the elastic membrane which produces aneurysms and accounts for the characteristic appearance on arteriogram. The aneurysmal dilatations tend to be larger and longer than those accompanying medial fibroplasia.

Medial fibroplasia is also not confined to the renal artery. Palubinkas and Ripley⁸ recently reported a celiac arterial lesion and we have observed the typical arteriographic features in the carotid arteries of a woman with bilateral renal arterial lesions. In our experience as in that of Wellington¹² and of Hunt and associates⁷ medial fibroplasia was present much more frequently in women than in men and in the middle decades of life often it was bilateral. On arteriograms it is distinguishable from subadventitial fibroplasia by the presence of aneurysms instead of areas of variable severe stenosis.

Subadventitial fibroplasia has been found in younger women than has medial fibroplasia. Curiously it is primarily a lesion of the right renal artery. Kaufman, Hanaford and Maxwell¹³ suggested that ptosis of the right kidney is in some way an etiologic factor but in patients whom we have studied ptosis did not seem to be an important feature. The affected kidney usually was considerably shorter than its mate indicative of the severity of the stenosis; the severity is further suggested by the abundant collateral circulation that is readily apparent. Although on the arteriograms there is evidence of bounding at the renal artery, this is an indication of varying degrees of stenosis and not of the presence of aneurysms.

There is a possibility that two types of fibromuscular hyperplasia exist—primary and secondary. The primary type would be represented by the fibromuscular hyperplasia with intact *elastica interna* such as we found in each of the 3 patients from 10 to 15 years of age. In the secondary type the hyperplasia would develop as a reaction to a dissecting hematoma of unknown cause.

We have not seen the periarterial fibrosis reported by Hunt and associates⁷ and by

Wood and Borges. Neither have we seen the inflammatory aortic and renal arterial lesions reported from South Africa¹⁴ and Singapore.¹⁵

The classification presented here provides a broader description of renal arterial lesions than has been possible in the past. It should permit accumulation of knowledge about the pathogenesis and natural history of these arterial diseases because they can now be recognized by arteriography. Furthermore this classification may help in selecting the appropriate operative procedures for each type of lesion thereby improving the results of surgical treatment for hypertension associated with renal arterial diseases.

Summary

A study of the macroscopic features of occlusive renal arterial lesions in 97 patients has shown the advantage of classifying these diseases according to their primary locations in the arterial wall and the types of tissue they comprise. Two lesions were primarily intimal: atherosclerosis and intimal fibroplasia and three were predominantly medial: medial fibroplasia, fibromuscular hyperplasia and subadventitial fibroplasia. This classification permitted a close correlation with renal arteriographic features.

Atherosclerotic lesions were either circumferential or eccentric plaques, sometimes complicated by thrombosis or dissecting aneurysm. They occurred predominantly in men. Arteriograms showed stenosis of the orifice with poststenotic dilatation; the presence of thrombosis or dissecting aneurysm was usually indicated by complete obliteration.

Intimal fibroplasia was characterized by fibrous intimal hyperplasia associated at times with disruption of the internal elastic membrane. Arteriographic features depended on the condition of this membrane when it was disrupted: an aneurysm formed producing an irregularly dilated artery.

Medial fibroplasia with aneurysms produced the string-of-beads arteriogram previously attributed to fibromuscular hyperplasia. The beads were aneurysms that developed because segments of the arterial wall were absent permitting focal dilatations. These thin segments alter

nated with ureis in which the media had been largely replaced by collagen. Muscular hyperplasia was not present.

Fibromuscular hyperplasia was an uncommon lesion resulting from increased amounts of fibrous and muscular tissue. It was sometimes accompanied by disruption of the internal elastic membrane. Arteriograms showed either symmetrical stenosis or when the internal elastic membrane was disrupted an irregularly dilated artery. We could find no arteriographic features that would differentiate this lesion from intimal fibroplasia.

Subintimal fibroplasia was characterized by dense collagenous thickening of the outer media irregularly replacing the muscular layer. It affected long segments of the renal artery. The arteriographic appearance was that of a severely stenosing lesion with regions of intense stenosis alternating with regions of lesser narrowing. This lesion has also been called fibromuscular hyperplasia because the variably severe stenosis produces an irregular arterial outline that suggests beading. This study shows subintimal fibroplasia to be distinct from fibromuscular hyperplasia as well as from medial fibroplasia which produces the string of beads arteriogram.

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Preoperative and postoperative electrocardiogram in complete transposition of the great vessels

George H. Khoury M.D.*

Reda W. Shaker M.D.

Rodney S. Fowler M.D.

John D. Keith M.D.

Toronto, Canada

With the recent advances in the surgical treatment of complete transposition of the great vessels¹ reevaluation of the electrocardiogram in this condition before and after creation of an atrial septal defect and after total correction with the Mustard procedure seemed to be warranted in order to examine the effect of these two different surgical procedures on the electrical activity of the heart.

Several authors²⁻⁷ have described the electrocardiogram in complete transposition of the great vessels in relation to the underlying pathology. Recently Shaher and associates⁸ referred to the hemodynamic findings in their cases to explain the different electrocardiographic findings. It is the purpose of this report to present the preoperative and postoperative findings in 30 cases of complete transposition of the great vessels.

Methods and material

The study comprised 30 patients with complete transposition of the great vessels admitted to The Hospital for Sick Children, Toronto, Canada. The diagnosis was con-

firmed by cardiac catheterization, angiocardiology, and surgery in all and by autopsy in 6. The ages of the patients ranged from 3 days to 17 years.

Serial preoperative and postoperative standard 12-lead electrocardiograms were obtained on each patient using the Sinhorn direct writer electrocardiograph. The diagnostic criteria used for atrial and ventricular hypertrophy are those of Keith and associates.⁹

Preoperative and postoperative vector cardiograms were recorded with the Frank lead system in 5 patients using the DR-9 Electronic for Medicine recorder. The findings will be presented briefly in illustrative examples. The patients were divided into two major groups.

Group I included 28 patients in whom an atrial septal defect was surgically created during the first month of life or later. The age at the time of operation is shown in Table I. This group was further divided into two subgroups according to the presence or absence of ventricular septal defect. *Subgroup Ia* included 16 patients with an intact ventricular septum. *Subgroup Ib* included 12 patients with a

* From the Department of Cardiology and the Research Unit, The Hospital for Sick Children, Toronto, and the Department of Paediatrics, University of Toronto, Canada.

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Reprint address: The Children's Hospital, 19th Ave., Downing, Denver, Colorado 80202.

ventricular septal defect one of whom had pulmonary stenosis.

Group II included 11 patients in whom complete repair was effected by the Mustard operation. Nine patients had an intact ventricular septum. 7 of these were from

Table 1 Age at time of creation of an atrial septal defect

Age	Number of patients
1 wk.	2
2 wk.	7
1 mo.	3
7 mo.	6
4 mo.	3
6 mo. 1 yr.	4
1 1/2 yr.	1
3 yr.	1
4 yr.	1

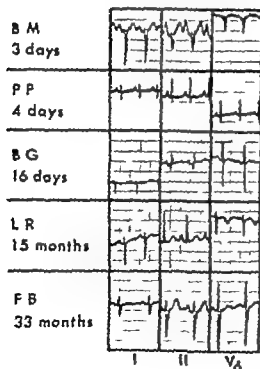


Fig. 1 Preoperative morphology of T wave in Leads I, II and V₆ in 5 patients with complete transposition of the great vessels. It varied from normal configuration in latest B.M. to flattening in Patients P.P. and B.G., inversion in Patient L.R. and dome shaped with notching in Patient F.B.

Subgroup 1a. One patient had undergone a Blalock-Tussing anastomotic procedure and one had a large atrial septal defect. Two patients were from Subgroup 1b.

Results

Group I Effect of surgical creation of atrial septal defect on the electrocardiogram: **REGULATIVE FINDINGS**

Rhythm Sinus rhythm was present in all patients. The P-R interval was within normal range in all; the average was 0.12 sec.

P Wave Right atrial hypertrophy was evident in 16 patients (56.6 per cent) as indicated by a peaked P wave with an amplitude of 2.5 mm or more. In the remainder of the patients the P wave was somewhat peaked but the amplitude was normal. The range of P wave duration varied between 0.04 and 0.08 sec with an average of 0.05 sec.

Mean QRS Axis in Frontal Plane The mean QRS axis showed a wide scatter in the frontal plane. In 20 patients it was directed to the right and inferiorly (right axis deviation, range +90 to ± 180 degrees). In 5 patients it was oriented to

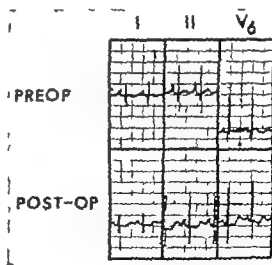


Fig. 2 Preoperative and postoperative electrocardiograms (Leads I, II and V₆) of Patient B.G. The preoperative tracing showed a flat T wave peaked P wave 5 mm in amplitude and deep Q wave. In the immediate postoperative tracing the P and Q wave diminished in amplitude and the T wave increased in magnitude.

the left and inferiorly (>0 degrees in 1 and 80 degrees in 2) and to the right and superiorly in 3 patients (-170 degrees in 3 and -120 and -110 degrees in the other 2).

Morphology of QRS Complex in Lead V_1
In Subgroup 1a an R_s pattern was found in 13 patients, a qR_s in 2, and an isolated tall R in 1 patient. In subgroup 1b an R_s pattern was noticed in 6 patients (>0 per cent) an R_s in 2, a tall R in 2, and an rS pattern in 1 patient.

Ventricular Hypertrophy In Subgroup 1a a pattern of right ventricular hypertro-

phy was present in 13 patients. In 1 patient combined ventricular hypertrophy was manifested by a Q wave in Lead V_1 over 2 mm in amplitude. In Subgroup 1b combined ventricular hypertrophy was present in 3 patients, and right ventricular hypertrophy in 7.

T Wave The morphology of the T wave in standard Lead I and left precordial leads was variable (Fig. 1). It was either flat, notched, dome shaped, or inverted. The amplitude was markedly small in all cases in Subgroup 1a, but in Subgroup 1b it was higher. The frontal T

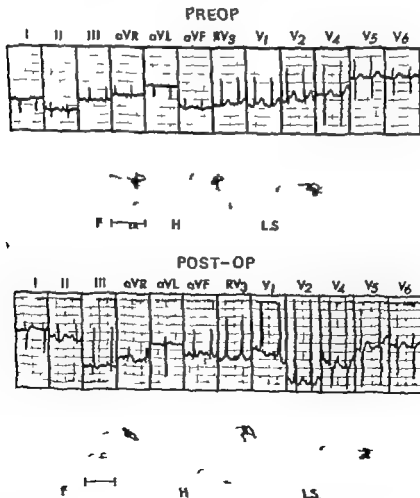


Fig. 3. The electrocardiogram (ECG) before and after creation of an atrial septal defect in a 6-month-old infant. Note the changes in both the P and T waves. In the postoperative electrocardiogram the P wave has become notched in Lead II and it has in Lead RV_3 and V_1 . The increase in the magnitude of the T vector is more apparent in the electrocardiogram.

vector was directed inferiorly either left ward or rightward (range of 30 to 120 degrees). The horizontal T vector was oriented anteriorly producing an upright T wave in right precordial leads.

POSTOPERATIVE FINDINGS The rhythm was nodal in 2 patients and normal sinus in the others.

The P wave became notched and its amplitude diminished in 26 of the 28 patients. Its duration was prolonged to an average of 0.085 sec. an increase of 0.035 sec. from the preoperative value (Fig. 2). In the right precordial leads the P wave became diphasic after being upright (Fig. 3). A pattern of combined atrial hypertrophy developed in 12 patients and left atrial hypertrophy in 11 and there was no change in 5 patients.

No change was noted in the direction of the mean QRS axis in the frontal plane or the duration of QRS complex.

In the right precordial leads an rR or rSR pattern was noted in 90 per cent of the cases.

Three patients in Subgroup 1a developed combined ventricular hypertrophy after an atrial septal defect had been created. In 2 patients a deep Q wave in Leads I and V_4 diminished in amplitude in the immediate postoperative period (Fig. 2).

T Wave The T wave increased in amplitude in 75 per cent of the cases. It became taller and assumed a normal configuration. This change was more noticeable in Subgroup 1a (Fig. 3). In the horizontal plane the T vector tended to rotate leftward and posteriorly producing a negative T wave in the right precordial leads. Serial examination of the electrocardiogram with increasing age in 4 patients showed that the T wave reverted back to its preoperative shape being either flat or inverted.

Group II Effect of total correction (Mustard operation) on the electrocardiogram Arrhythmias was commonly noted in the immediate postoperative period (Fig. 4). Nodal rhythm was observed in 5 patients. Atrial flutter developed in 5 patients but responded quickly to digitalis therapy. One patient had nodal tachycardia with intraventricular conduction defect (Fig. 4).

The P wave diminished in amplitude and its configuration was altered. It appeared

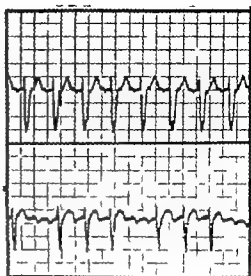


Fig. 4 Standard Lead II. Postoperative arrhythmias in 2 patients after total correction. The upper tracing (R, 12 years old) is an example of atrial flutter with 2:1 block or it could be a nodal tachycardia with retrograde 2:1 block. Note the inverted notches on the upstroke of the T wave which step out exactly with the obvious inverted F waves. The lower tracing (B.G. 2 years old) is an example of atrial flutter.

flat in 9 patients (Fig. 5) and in 2 patients it was dome shaped. The PR interval was prolonged in 3 patients (0.18 sec. in 2 and 0.20 sec. in 1) but was within normal limits in the other patients.

The T wave increased in magnitude and was upright in 8 patients, diphasic in 2 (Fig. 5B) and inverted in 1 after being upright. In 2 patients the electrocardiogram 18 months postoperatively showed the T wave to be diphasic in Leads I and V_4 after being upright.

Discussion

The electrocardiographic picture in complete transposition of the great vessels is variable depending on the underlying pathophysiology.¹⁻⁴ Right ventricular hypertrophy is the usual pattern in cases with intact ventricular septum and low pulmonary vascular resistance whereas combined ventricular hypertrophy is common in the presence of ventricular septal defect and elevated pulmonary vascular resistance.

The resultant physiologic effect after surgical creation of atrial septal defect as

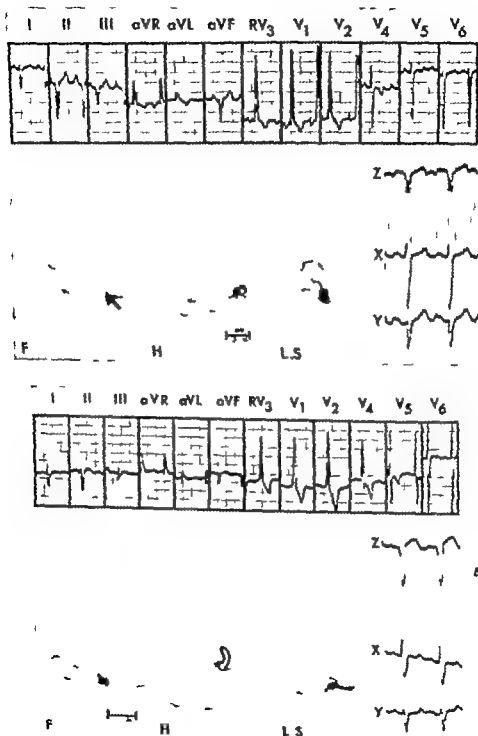


FIG. 5A The preoperative electrocardiogram and vectorcardiogram of a 12-year-old boy with complete transposition of the great vessels who underwent a Blalock-Taussig anastomosis procedure for cyanosis. The F loop is suggestive of combined atrial and right ventricular hypertrophy.

FIG. 5B The electrocardiogram and vectorcardiogram of the same patient as in Fig. 5A after total repair with Mustard operation. Notice the flattening of the P wave on the standard and orthogonal lead. The R wave in Leads V₁ and V₂ returned to a relatively normal amplitude. In the horizontal plane the description of the QRS loop is clockwise and the loop is displaced more to the left than preoperative.

demonstrated by Shaker and Kidd¹⁰ are an increase in the degree of bidirectional shunting at the atrial level, improvement in the systemic arterial saturation, increase in the systemic blood flow, and a diminution in the calculated pulmonary blood flow.

Electrically, this was manifested by changes in cardiac depolarization and repolarization.

In the preoperative electrocardiogram, right atrial hypertrophy was noted in 76 per cent, whereas postoperative notching, prolonged duration and diminished amplitude of the P wave were observed in 90 per cent. These P wave changes suggestive of combined or left atrial enlargement could represent an actual increase in atrial work secondary to a step up in bidirectional shunting. Against this hypothesis is the fact that the left atrial pressure in 60 per cent of the group of patients studied by Shaker and associates remained essentially unchanged after creation of the atrial septal defect. Moreover, the diminution in the calculated pulmonary blood flow exceeded the increase in the bidirectional shunt at the atrial level. Alternatively, these P wave changes could have been due to the traumatic effect of surgical excision of the atrial septum.

Several authors^{8, 9, 11} described the T wave changes noted in this study in Standard Lead I and the left precordial lead. It was suggested that the flat and inverted T wave could be due either to excessive pulmonary blood flow with overloading of the left ventricle or to myocardial ischemia. After the creation of an atrial septal defect the T wave increased in magnitude and became upright in the majority of patients. Such changes are most likely due to the rise in systemic arterial saturation with better oxygenated perfusion of the myocardium.

The appearance of an rR or rsR pattern in the right precordial leads of the postoperative electrocardiogram in Group I is of significance since it indicates volume overloading of the right ventricle secondary to the increase in systemic blood flow. Diminution in the calculated pulmonary blood flow was suggested by the decrease in the magnitude of the Q loop in Leads I and V₁.

The Mustard operation in patients with complete transposition of the great vessels involves excision of the atrial septum and the insertion of a pericardial baffle in such a way as to divert the pulmonary venous return into the right ventricle and the systemic venous blood flow into the left ventricle. The prolonged P-R interval and flattening of the P wave seen in the electrocardiogram after total repair is due to surgical trauma.

No marked changes were observed in ventricular hypertrophy patterns after total correction. One expects a change only if complications occur such as pulmonary venous obstruction or progression of pulmonary vascular disease.

Arrhythmias were commonly observed in the immediate postoperative period but these were transitory and responded to medical therapy.

Summary

The electrocardiograms of 30 patients with complete transposition of the great vessels were analyzed before and after surgical creation of an atrial septal defect and after total repair with the Mustard procedure. The effect of surgery was manifest in changes in the I and T waves and to a lesser extent in the ventricular hypertrophy pattern. Arrhythmias were commonly noted in the immediate postoperative period.

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Valvular heart disease in the monkey (*Macaca mulatta*)

William C. Roberts MD*

J P M Innes ScD (Cantab) MFCVS FCP Path

Bethesda Md

In contrast to the very high incidence in man cardiac diseases in animals constitute a small percentage of their total diseases. Despite their infrequency however cardiac diseases occur in almost all animal species. Most reports of spontaneous cardiac disease in animals have concerned dogs cats and horses probably because these species are most frequently observed and their life spans are relatively long.

Among the cardiovascular diseases found in monkeys systemic hypertension appears to be the most frequent and arteriosclerosis among the least common.¹ Myocardial infarction is extremely rare in monkeys although electrocardiographic evidence of coronary arterial insufficiency is occasionally present and small focal myocardial scars are occasionally seen at necropsy. Acute and chronic endocarditis has been reported rarely in monkeys.²⁻⁴ Scott² in 1927 and Hamerton^{3,4} in 1939 each described a human case of polypoid ulcerative endocarditis with systemic emboli. Several years later Hamerton⁵ described sclerosis of the cardiac valves of 2 old baboons but few details were given. Lapin and Yakovlev⁶ described 2 monkeys which had mitral stenosis and

regurgitation and diffusely scarred contracted and fused mitral leaflets and chordae tendineae. The etiology of the mitral disease in these monkeys was not determined but the authors believed that infective endocarditis which had healed was the most likely explanation. In addition these investigators described 4 other monkeys which had acute endocarditis of the mitral valve and in 1 a large polypoid vegetation was present. Among over 1000 animals necropsied during the past 18 months at the Biometrics Research Laboratories† 2 were found to have valvular cardiac disease. One of these monkeys had a scarred mitral valve which was both stenotic and incompetent and the second had acute endocarditis of both mitral and aortic valves leading to aortic stenosis. A description of the clinical and pathologic findings in these 2 monkeys forms the basis for this report.

Clinical and necropsy observations

Monkey 1 (65566) The monkey was an adult breeding female (exact age uncertain) which arrived pregnant later aborted and still later had a live baby. Available clinical data are meager. Fig. 1 is an elec-

From the Laboratory of Pathology Clinical Surgery National Heart Institute at National Institutes of Health Bethesda Md and the Biometrics Research Laboratory, Pathology Branch, National Cancer Institute, Bethesda Md.

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*Visiting Chief, Laboratory of Pathology, Clinical Surgery National Heart Institute, National Institutes of Health, Bethesda Md 20014.

†These monkeys included mature males and females mostly M and female.

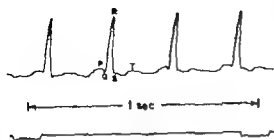


Fig 1 Monkey 1 Lead II of the electrocardiogram recorded approximately 12 hours before death in a monkey with mitral valvular disease



Fig 2 Monkey 1 Exterior of the heart The left atrial appendage (LAA) severely dilated and totally obscures the pulmonary trunk Both the right (RI) and left (LI) ventricles are enlarged as is the right atrial appendage (RAA) The right middle lobe (RML) of the lung is collapsed and histologic sections disclosed a hemorrhagic infarct T Trachea A Ascending aorta



Fig 3 Monkey 1 Left atrium Top The left atrium (LA) extremely dilated thin walled and free of clot Just above the mitral valve the endocardium is focally thickened probably secondary to a jet lesion of mitral regurgitation The leaflets of the mitral valve are thickened particularly the margin and the chordae tendineae are short and thick A small perforation in the posterior half of the anterior mitral leaflet is indicated by the arrow Close-up view of the opened mitral valve The cut transect the posterior (P) leaflet A Anterior leaflet Bottom The mitral valve as seen from the left atrium before it was opened The orifice of the valve more or less fixed and it was probably changed little during the cardiac cycle The valve is both stenotic and incompetent

trocadiogram recorded about 12 hours before death when the monkey was in a state of severe congestive cardiac failure with ascites and tachycardia (220 beats per minute) Despite massive left atrial dilatation sinus rhythm was present Shortly after the electrocardiogram was made the monkey was given digoxin and several hours later the heart rate was approximately 125 beats per minute The animal died shortly thereafter

At necropsy large quantities of fluid were present in the pleural and peritoneal cavities and the liver was firm and nodu



Fig 4 Monkey 1 (Photomicrograph of mitral valve and left atrium). Left: The section includes the anterior mitral leaflet (AML), mitral annulus (ML), left atrial (LA) wall, an aortic valve (AO) cusp, and ascending aorta (AA). The thickening of the mitral valve is due entirely to proliferation of fibrous tissue. Various channels are present in the thickened mitral leaflet. Right: Section of left atrial wall shows severe hypertrophy and dilation of myocardial fibers. No vacuolization or inflammatory cell were numerous in the left atrial tissue (H&E) (left) hematoxylin and eosin $\times 135$ (right).

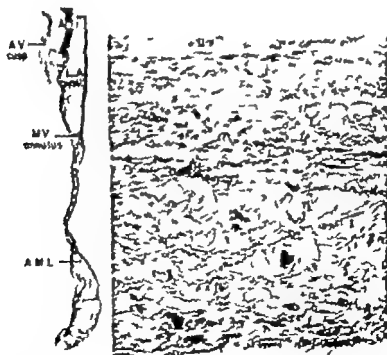


Fig 5 Monkey 1 (Photomicrograph of mitral valve and left atrium). Left: The section includes the anterior mitral leaflet (AML), mitral annulus (ML), left atrial (LA) wall, an aortic valve (AO) cusp, and ascending aorta (AA). The thickening of the mitral valve is due entirely to proliferation of fibrous tissue. Various channels are present in the thickened mitral leaflet. Right: Section of left atrial wall shows severe hypertrophy and dilation of myocardial fibers. No vacuolization or inflammatory cell were numerous in the left atrial tissue (H&E) (left) hematoxylin and eosin $\times 135$ (right).

lar. The kidneys were normal. Cultures of the heart blood and mitral valve grew only contaminants.

The heart was markedly enlarged (Fig. 2). The mitral valve was contracted, fibrotic, and both stenotic and incompetent (Figs. 3a). A small smooth-walled perforation which probably was of little hemodynamic significance was present in the anterior mitral leaflet. All cardiac chambers were dilated; the left atrium to unusual proportions, and both ventricles were hypertrophied. The aortic and pulmonary valves were normal, as were the tricuspid valvular leaflets and chordae tendineae, but the tricuspid annulus was dilated (Fig. 6). The marked dilatation of the right atrium suggested that the tricuspid valve, although anatomically normal, was functionally incompetent. Additional evidence is provided by the severe centrilobular hepatic congestion and necrosis (Fig. 6).



Fig. 6 Monkey 1. Right side of the heart and liver. Left: Opened right atrium (R4) inferior vena cava (IVC dashed line) tricuspid valve and right ventricle (R1). The right atrium coronary sinus ostium (CS) and tricuspid valve ring are markedly dilated apparently the result of relative tricuspid regurgitation which in turn was secondary to the presumed pulmonary hypertension. Right: Photomicrograph of liver showing severe centrilobular congestion and necrosis. The type of hepatic changes is characteristically seen in severe right sided cardiac failure. Hematoxylin and eosin $\times 65$.

Histologic sections showed only fibrous thickening of the mitral valvular leaflets. No Aschoff bodies were seen in any of the multiple sections of the heart. The myocardial fibers of all cardiac chambers were hypertrophied and in addition many of those in the left atrium were degenerated. Inflammatory cells were not present in the myocardium or mitral valve. The pulmonary veins and alveolar capillaries were distended and congested. Neither the pulmonary arteries nor veins had thick walls.

Monkey 2 (651635) The animal belonged to an untreated control group of *Macaca mulatta* and had been under observation at Biometrics Research Laboratories for 6 months. A tuberculin skin test performed when the animal arrived was negative. The animal had diarrhea periodically but multiple bacteriologic and parasitologic examinations of the feces were unremarkable.

The cardiac changes observed at necropsy are described in detail in Figs. 13. In summary there was diffuse adhesive fibrous and fibrinous pericarditis diffuse

inflammatory thickening of the aortic valvular cusps causing aortic stenosis, similar inflammatory thickening of the anterior mitral leaflet but probably no mitral stenosis or incompetence, myocarditis with focal abscess formation and vasculitis and severe left ventricular hypertrophy. Sections of the valvular cusps, pericardium and myocardium which were stained for pyogenic and tuberculous bacteria, fungi and spirochetes were negative. No Aschoff bodies were seen in the sections of heart. In addition to the cardiac findings there was diffuse acute pulmonary edema but no hydrothorax or ascites. Multiple disseminated lesions of pulmonary ascaris also were present.

Comments

The etiology of the valvular heart disease in each of these monkeys is speculative. Neither organisms nor Aschoff bodies were found in histologic sections of the hearts in either animal. Indeed rheumatic disease of the heart with Aschoff bodies has never been reported in domestic animals. In some respects the appearance of the mitral

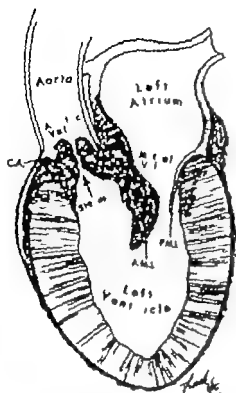


Fig. 7 Monkey 2 Diagram of heart. The aortic aortic valve and the anterior mitral leaflet (A.V.L.) are markedly thickened and the aortic aorta is stenotic. The posterior mitral leaflet (P.V.L.) is normal. The inflammatory process (dark shading) also involved the atrial wall, left ventricular wall and pericardium. The inflammation involving beneath the proximal portion of the left coronary artery (C.A.) causes narrowing of this vessel.

valve in Monkey 1 resembles rheumatic mitral disease in human beings in that the scarring process was diffuse involved both leaflets as well as all chordae tendineae and was most pronounced at the margins of the leaflets. The presence of valvular chordae in the scarred mitral leaflets in Monkey 1 is no indication of a rheumatic etiology since in human beings vessels may be seen in mitral valves altered by congenital malformations, trauma and in Marfan's syndrome as well as by rheumatic fever and vessels are present normally in cardiac valves in some monkeys.¹ Severe degeneration of the myocardial fibers of the atria in this animal is more in favor of a rheumatic process since this disease always involves the left atrial wall¹⁰ but it is possible that chronic left atrial dilatation from any cause would produce a similar change. The perforation in the anterior mitral leaflet in this monkey also is difficult to explain on the basis of rheumatic disease. An infection which subsequently healed appears to be the most reasonable explanation of the perforation and possibly also of the diffuse scarring of the leaflets.

The etiology of the pericarditis in Monkey 2 is purely speculative. The anatomic appearance of the valvular lesions in this animal seems to be unique and we are not



Fig. 8 Monkey 2 Opened heart. Left: The left ventricle (L.V.), aortic valve (A.V.) and aorta are opened. Each of the three aortic cusps is thick, as is the anterior mitral leaflet (A.V.L.). The focal area of acute inflammation (black) beneath the left coronary artery (L.C.A.) is indicated. P.T. Pulmonary trunk. Right: The opened left atrium (L.A.), mitral valve and left ventricle are shown. The anterior leaflet (A.V.L.) is diffusely thickened and the posterior mitral leaflet (P.V.L.) is normal.



Fig. 9. Monkey 2. Exterior of heart (left) and transverse section of ventricles (right). The vi-ceral pericardium is shaggy. The left ventricular wall (L.V.) is markedly hypertrophied. R.V. Right ventricle. P.A. Right atrial appendage. L.A. Left atrial appendage. Ao. Ascending aorta. P.T. Pulmonary trunk. V.S. Ventricular septum.



Fig. 10. Monkey 2. Photomicrographs of the aortic and mitral valves. Left. Section includes a thickened aortic valvular cusp (11), the thickened anterior mitral leaflet (A.M.L.) and the normal posterior mitral leaflet (P.M.L.). The left atrial (L.A.) and left ventricular (L.V.) walls and coronary artery (C.A.) are indicated. This section illustrates the continuity of the aortic valve, anterior mitral leaflet and left atrial wall. The inflammatory process involved all of these structures. A close-up of the area within the rectangle constitutes Fig. 11. Right. A close-up of the anterior and posterior mitral leaflets. Hematoxylin and eosin. $\times 4.5$ (left) $\times 12$ (right).



Fig. 11. Monkey 2. The area within the rectangle in Fig. 10. A band of necrotic debris is present in the upper portion in addition to numerous inflammatory cells. Several fragments are present in the upper portion of the aortic area within the rectangle, constituting Fig. 12. Hematoxylin and eosin stain $\times 19$.



Fig. 12. Monkey 2. Area of aortic aortic valve cusp marked by rectangle in Fig. 11. Collections of acute inflammatory cells and necrotic debris are present. Hematoxylin and eosin stain $\times 260$.

in one of a previous report describing a necrotizing, inflammatory process of similar distribution in either man or monkey. Each of the cusps of the aortic valve in this monkey were diffusely and uniformly thickened in the inflammatory process but only the anterior cusp of the mitral valve was involved the posterior one being entirely normal. Since the anterior mitral leaflet is continuous with the aortic valve leaflets it would appear to be reasonable to assume that the necrotizing, inflammatory process extended directly from one valve to the other. Whether this process began in the endocardium of these cardiac valves on the left side and subsequently spread by direct extension to the adjacent myocardium and finally to the subpericardial adipose tissue and pericardial surfaces or whether the process initially began in the pericardium and spread inward is not known. That the endocardial surfaces of the involved aortic and mitral leaflets are smooth is some evidence that the process did not begin as a vegetation but as a process within the valve leaflets.



Fig. 11 Monkey 7. Acute pericarditis and myocarditis. Left: Section of subepicardial blood vessel in which acutely inflamed. Right: Section of left ventricle demonstrating focus of acute inflammation. Hemosterythia and eosinophils. $\times 175$ (left) $\times 660$ (right).

At autopsy there was no evidence of mediastinitis. Frank areas of fibrinoid necrosis were present within the aortic and mitral leaflets and the rings of each of these valves contained abscesses. Similar acute inflammatory cell were present within the valve leaflets myocardium and pericardium. Although the predominant cell appeared to be the polymorphonuclear leukocyte the inflammatory process must have been present for some time as evidenced by the severe left ventricular hypertrophy.

Summary

Valvular heart disease of unknown etiology is described in each of 2 monkeys. One had chronic scarring of the mitral valve which was both stenotic and incompetent and the second had acute necrotizing inflammation of the aortic valve which was stenotic and of one cusp of the mitral valve.

The photomicrographs were taken by M. Gebhard Groll.

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The temporal sequence of lymph flow in the right lymphatic duct in experimental chronic pulmonary edema

H N Ashley MD*

S E Leeds MD

J J Sampson MD

N Rudo MD

M Friedman MD

San Francisco Calif

In 1942 Warren and Drinker¹ measured pulmonary lymph flow in dogs with acute pulmonary edema produced by compression of the pulmonary veins and observed that lymph flow increased. Studies by Rabin and Meyer² and in our laboratory^{3,4} confirmed that pulmonary lymph flow increased with elevation of left atrial pressure; however these increases were insufficient to prevent the development of overt pulmonary edema. We subsequently devised a technique for the development of chronic heart failure in dogs⁵ and demonstrated that in chronic failure the right lymphatic duct channels which drain nearly all of the canine lung⁶ expand and gross increases in pulmonary lymph flow occurred. The current study attempts to determine the time sequence involved in the expansion of the pulmonary lymphatic channels and the concomitant rise in pulmonary lymph flow in the development of heart failure.

Methods

Eighteen mongrel dogs weighing between 12 and 20 kilograms were used in this study. They were anesthetized with intravenous sodium pentobarbital (29 mg per kilogram) and a side to side 7 to 10 mm aortocaval anastomosis was made below the renal vessels by approximating and suturing the aorta and veni cavae. The animals were given 25 mg of desoxy corticosterone trimethylacetate⁷ twice a week and were placed on a salt enriched diet of approximately 6 Gm of salt per day.

In the first group of 8 animals lymph from the right lymphatic duct was collected immediately prior to and 1 day after the A-V fistula operation. In another group of 5 dogs the lymph flow was observed 10 days after the operation. In a third group of 5 dogs lymph flow was observed 20 days after the operation and a single animal was studied 28 days after the operation.

With the technical assistance of Shost J J, Pat J B S, and V de H Wm, R N.

From the Department of Experimental Surgery and Pathology and the Medical Branch of the University of California, San Francisco, Calif.

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Address reprint requests to Dr. Ashley, 1600 Divisadero St., San Francisco, Calif. 94115.

*Presently in Chile.

On the day on which the animals were studied they were anesthetized with intra-venous pentobarbital (29 mg per kilo gram) placed on an intermittent positive pressure respirator and given 3 to 5 cc of 2 per cent Evans blue dye intratracheally. Lymph from the lungs was collected by an improved technique recently developed in this laboratory,⁷ which permitted continued collection on the following day in the unanesthetized dog if so desired. The right external jugular vein was exposed and a segment of that portion which contained the entrance of the right lymphatic channels was isolated with umbilical tape ligatures. Venous tributaries leading into the segment were also ligated. The cephalad end of the isolated vein was cut and fitted over a small polyethylene cannula. After the residual blood was aspirated the incision in the skin was closed and lymph flowing into the venous segment was collected. In this manner it was possible to use the external jugular vein as a fistula for the serial collection of lymph from the right lymphatic duct.

In the first group of 8 dogs the method was utilized to collect lymph from the unanesthetized animal 1 day postoperatively but in the remaining group the dogs were anesthetized. Lymph flows were obtained and after thoracotomy left atrial pressures were recorded by inserting a tube attached to a manometer into the left atrial appendage. After pressure was measured lung biopsies were obtained and the respirator was stopped. Necropsy was performed immediately and pulmonary edema was estimated by the gross appearance of the lungs and the ratio of lung weight to body weight.⁸ Cardiomegaly was estimated by the ratio of heart weight to body weight.⁹

Results

The mean preoperative flow was 5 ml per hour (4.62) and 1 day postoperatively the mean flow was 9 ml per hour (4.913) (Fig 1). These animals did not demonstrate any signs of acute heart failure.

In the group of animals studied 10 days postoperatively edema of the hind limb

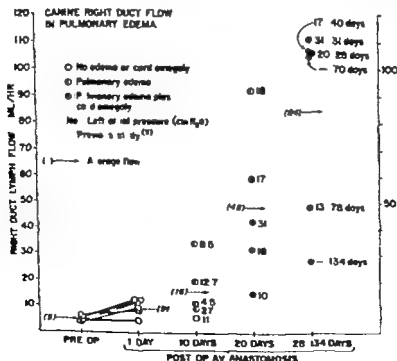


Fig 1 The temporal sequence of lymph flow in the canine right lymphatic duct in experimental chronic pulmonary edema. Note the increased increments in mean flow in the right lymphatic duct after the tenth day.

Electrocardiographic cancellation

A study of a single dipole at variable locations

Robert A. Helm MD
Te Chuan Chen MD
Cincinnati Ohio

Electrocardiographic cancellation provides a technique which has been used rather extensively to investigate the validity of representing the heart as a single dipole variable in strength and axial orientation but constant in location.¹⁻⁹ The conclusions drawn from such studies have been conflicting. It is the purpose of this paper to clarify the significance of electrocardiographic cancellation by reporting computations of cancellation patterns obtained when the location of a single dipole varies in a well defined manner with each change in dipole strength and axial orientation. These computations were carried out by means of previously described mathematical techniques.¹⁰

Methods

Fig 1 represents the basic model utilized in this study and will hereafter be designated as Model I. The location of the dipole is postulated to move through a distance of 1 cm at 4 msec intervals. The locations of the dipole at each of these time intervals are arbitrarily placed at one of the dipole points on the transverse plane of Frank's model¹¹ and these are depicted and labeled in Fig 1. The arbitrarily chosen magnitudes of the X and Z components of the dipole

at each location are also given in milliamperes in Fig 1. All of the dipole orientations are such that there are no Y components.

Fig 2 represents a modification of the basic model in which all of the consecutive dipole locations as well as the orientation of the dipole at each location have been rotated counterclockwise through 90 degrees. Comparison of Figs 1 and 2 will clarify the differences between these models. The model depicted in Fig 2 will hereafter be designated as Model II.

The x and z components of the image vectors for each of the dipole locations are those published by Frank (see appendix of Reference 11). The polarities of Frank's z components are reversed, however, in order that lead polarity might be identical with that of conventional precordial leads. Frank's data were normalized and converted to mv/mA-cm in accordance with the methods described in the appendix of Reference 11.

Figs 3 and 4 represent the scalar patterns obtained with various leads with Models I and II respectively. In the inserts of Figs 3 and 4 are diagrams of Frank's transverse plane showing the location of the 6 cm square along the periphery of which the dipole migrates 1 cm every 4

¹⁰ at the Cardiac Laboratory, Cincinnati General Hospital and the Division of Medicine, College of Medicine, University of Cincinnati, Cincinnati, Ohio.
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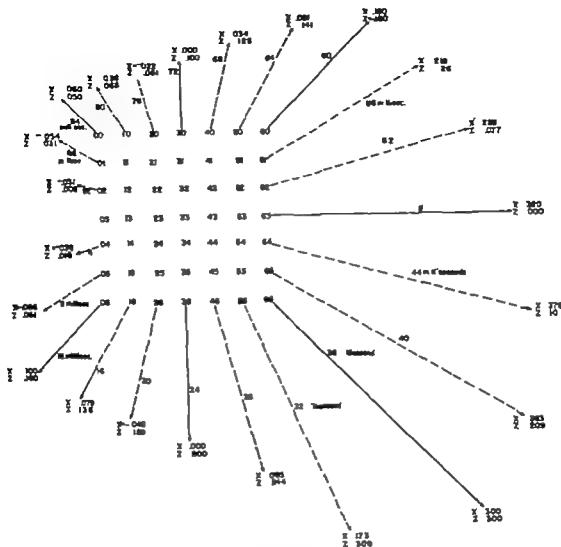


Fig. 1 The basic model referred to in the text as Model I depicts the magnitude of the X and Z components of the variably located dipoles in $\text{mV}\cdot\text{cm}$. The dipole moves through a distance of 1 cm at 4 msec intervals. The numbers constituting the 6-cm square refer to the dipole locations on the transverse plane of Frank. Model I the x and z components of the image vectors for each of the dipole loci on are listed in the appendix of Reference 11.

msec Leads are formed by determining the differences in potential which would exist at each 4 msec interval between any of the 16 points A through P located on the boundary of the transverse section. Each such difference in potential represents the sum of the product of the X component of the dipole vector and the x component of the lead's image vector and the product of the Z component of the dipole vector and the z component of the lead's image vector.

As developed in the previous publication¹⁰ the general equation for an electrocardiographic cancellation may be written as

$$R = P - Q(q_1 L_1 + q_2 L_2 + q_3 L_3 + q_4 L_4)$$

where R is the cancellation voltage, P is the voltage of the lead being cancelled, and the L terms represent the voltages of the leads which are summated to produce the cancellation. All of these voltages vary with time. The Q and q terms are coefficients

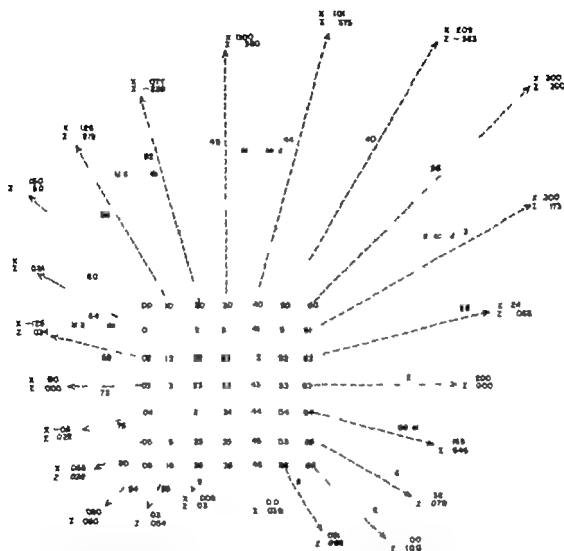


Fig. 2. The basic model illustrated in Fig. 1 has been modified and is referred to in the text as Model II. The consecutive dipole locations have been rotated counterclockwise through 90 degrees and the orientation of the dipole at each location has also been rotated counterclockwise through 90 degrees.

which remain constant throughout the entire cardiac cycle or any designated portion of it. Q may have any positive or negative value but $(q_1 + q_2 + q_3 + \dots + q_n) = 1$ in all instances.

As an example of the application of this equation, the voltages of the four points C, G, H, and O depicted in the inserts of Figs. 3 and 4 may be considered. Let $P = (C, H)$, $I_1 = (O, H)$ and $L = (G, H)$ where the letter designations of the points in question are also used to represent their voltages. Then

$$R = (C, H) - Q_1 q_1 (O, H) + q_2 (G, H) \quad (1R)$$

representing what will be referred to in this paper as an R cancellation.

Considering again the voltages of the four points C, G, H, and O in conjunction with the general cancellation equation let $P = (C, O)$, $L_1 = (C, H)$ and $L = (G, O)$. If for convenience of notation R is replaced by the small case letter r

$$r = (C, O) - Q_1 q_1 (C, H) + q_2 (G, O)$$

where Q_1 , q_1 , and q_2 are coefficients having different numerical values but the same significance as in Equation (1R). Let $Q_1 q_1 = m$ and $Q_2 q_2 = n$. With rearrangement

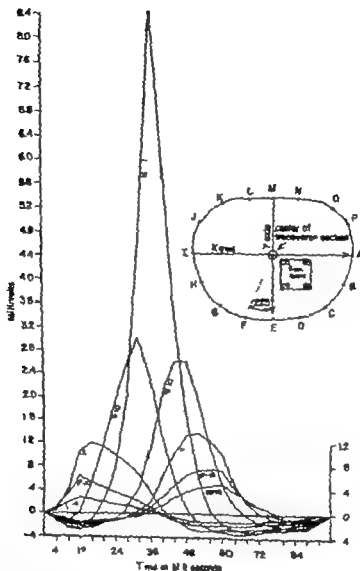


Fig 3 The insert depicts the position on the transverse plane of the 6-cm square about which the dipole migrates in Figs 1 and 2. The points A through P on the periphery of the transverse plane indicate the location of electrodes. The graphs represent the difference in potential between various electrode pairs calculated from the centres of Model 1 (Fig 1) in conjunction with the measured error data published by Frahm.

$$r = [(1 - m)C + mK] - [I - aJ + aG] \quad (1r)$$

representing what will be referred to in this paper as an r cancellation.

The following four point R cancellations were explored in this study in addition to that expressed by Equation (1R).

$$R = (C h) - Q q (P h) + q (F h) \quad (2R)$$

$$R = (C h) - Q q (A h) + q (F h) \quad (3R)$$

$$R = (C h) - Q q (B h) + q (D h) \quad (4R)$$

The following four point r cancellations

were utilized in this investigation in addition to that expressed by Equation (1r).

$$r = [I - m)C + mK] - [I - a)P + a)F] \quad (2r)$$

$$r = [I - m)C + mK] - [I - a)A + a)F] \quad (3r)$$

$$r = [I - m)C + mK] - [I - a)B + a)D] \quad (4r)$$

The following R cancellation involving more than 4 points on the surface of 1 rank transverse plane was also studied.

$$R = (C h) - Q q (O h) + q (G h) + q (H h) \quad (5R)$$

Another form of cancellation arbitrarily

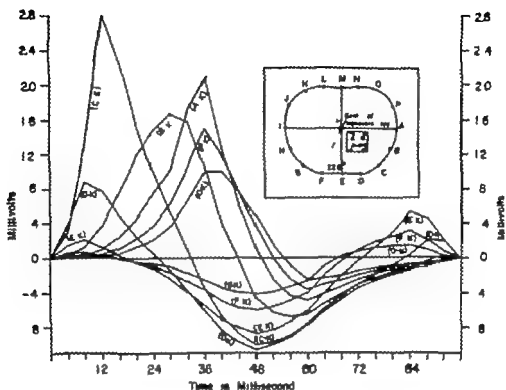


Fig. 4 This illustration corresponds to that of Fig. 3 except that the graphs are based on Model II rather than Model I

designated as an R type may be derived as follows. Let L_1 , L_2 and L_3 represent three separate leads which possess perfectly uniform although not necessarily orthogonal lead fields.¹² Substituting in the general equation for an electrocardiographic cancellation

$$R = P - Q(qL_1 + q_2L_2 + q_3L_3)$$

where Qq_1 , Qq_2 and Qq_3 become unique constants when the series of R' potentials is minimized by one of the techniques described in the previous publication.¹⁰ The R' deflections then represent the minimal residual voltages resulting from the fact that the field of lead P is not uniform. Let $L_1 = (\lambda x_1 + \gamma y_1 + Zz_1)$, $L_2 = (\lambda x_2 + \gamma y_2 + Zz_2)$ and $L_3 = (\lambda x_3 + \gamma y_3 + Zz_3)$ where λ , γ and Z are the time varying components of the moving dipole and the nine lower case symbols are all separate constants as the result of the uniformity of the lead fields of L_1 , L_2 and L_3 . Then

$$R = P - (\lambda x + \gamma y + Zz) \quad (R')$$

where x , y and z must consequently also

be unique constants when the series of R potentials is minimized. (The significance of the quantities x , y and z and their relation to the components of the image vector of the fixed location of an equivalent dipole will be considered in the Discussion.) Since Models I and II of the present study do not possess Y components the last equation is herein utilized in the following two dimensional form to assess the uniformity of the field of lead (C h)

$$R = (C h) - (\lambda x + Zz) \quad (IR')$$

The foregoing equations are listed in this section to permit their recognition in the following sections by means of their marginal parenthetical designations. The symbols R , r and R' can be furthermore defined by the subscripts r and s depending upon whether the residual voltages are calculated as a minimum range cancellation or a minimum root mean square cancellation respectively. (Reference to the previous publication¹⁰ will clarify the differences between these two types of cancellation patterns.)

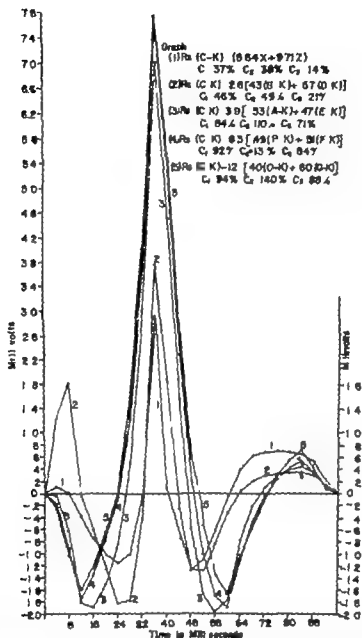


Fig. 5 The minimum root mean square cancellations were calculated for Model I. Graph 1 represents the residual voltages resulting from the lack of uniformity of the field of lead (C h). Graphs 2, 3, 4 and 5 illustrate the residual voltages when lead (C h) is cancelled by combinations of leads (B h) and (D h), of leads (A h) and (E h), of lead (P h) and (F h), and of leads (O h) and (G h) respectively.

1 and 2 respectively. It is apparent from inspection that these graphs represent residual voltages which are considerably smaller than the voltages of the R cancellations depicted by the graphs of Figs 3 and 6. It is of interest that the magnitudes of the voltages of the cancellations illustrated in Figs 7 and 8 decrease as the

electrodes adjacent to point C are moved to locations more distant from this point. Despite this diminution the corresponding cancellation coefficients c_1 , c_2 and c_3 in curve or remain approximately constant. However, the cancellation coefficient c_1 decreases in the same manner as the cancellation voltages diminish when the electrodes

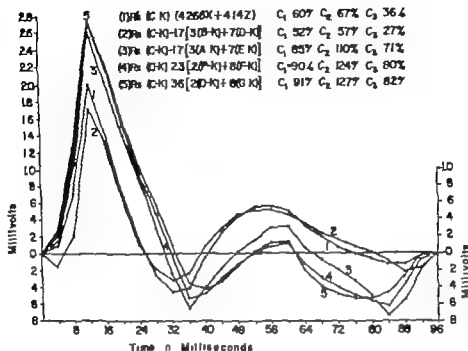


Fig 6 The illustration correspond to that of Fig 5 except that the graphs are based on Model II rather than Model I

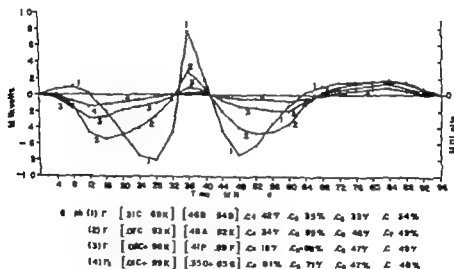


Fig 7 Graphs 1 through 4 represent minimum root mean square cancellation based on Model I

adjacent to point C are moved to locations more distant from this point

Figs 9 through 11 were computed after various modifications of Model I. Only 7 instants of time at 12 msec intervals were considered. The dipole vectors at these in-

stants are depicted by solid rather than by dotted lines in Fig. 1. Moreover the locations of the dipole at these instants of time are not shown in Fig. 1 but are listed in Figs 9 through 11. The graphs illustrated in Figs 9 through 11 represent

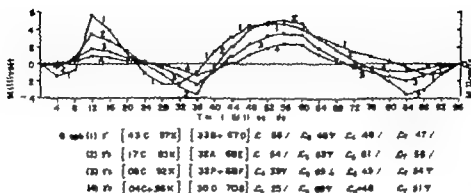


Fig. 2 Graphs 1 through 4 represent minimum root mean square r cancellations based on Model II

minimum range cancellations. Although they are not illustrated minimum root mean square cancellations were also computed and their various coefficients are listed in the equations given within the brackets in Figs. 9 through 11.

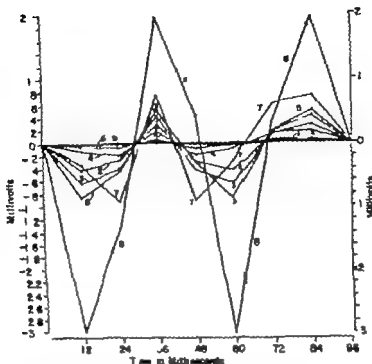
For construction of Fig. 9 the dipole migrates about the boundaries of three separate 2 cm squares. The corners of these squares are formed by locations 02, 22, and 00 for Graphs 1 through 3, by locations 24, 44, and 22 for Graphs 4 through 6, and by locations 46, 66, 64, and 44 for Graphs 7 through 9, respectively. Reference to Fig. 1 shows that although the distance traversed by the migrating dipole is the same for these 3 groups of graphs, the 2-cm square is located most centrally for Graphs 1 through 3, most peripherally for Graphs 7 through 9, and in an intermediate position for Graphs 4 through 6. Lead field theory¹² would indicate that the field of lead (Ck) should become progressively less uniform as the 2 cm squares along the boundaries of which the dipole migrates assume progressively more peripheral locations. This is confirmed in Fig. 9 by the R cancellations of Graphs 1, 4, and 7, which show increasing voltage deflections and also by their respective cancellation coefficients: e.g., C_1 increases from 5.7 to 11 to 18 per cent.

With the use of the same 4 points (C, G, K, and O) in all instances, both R and r cancellations were computed and are illustrated in Fig. 9. As the uniformity of the field of lead (Ck) decreases, the R cancellations represented respectively by Graphs 2, 5, and 8 demonstrate increasing voltage

deflections and increasing cancellation coefficients: e.g., C_1 increases respectively from 32 to 38 to 58 per cent. In contrast, as the lead field of (Ck) becomes less uniform, the r cancellations represented respectively by Graphs 3, 6, and 9 show decreasing voltage deflections. With such decreasing deflections, the cancellation coefficient c_1 decreases, whereas the cancellation coefficients c_2 , c_3 , and c_4 remain approximately constant or increase.

For Fig. 10 the dipole migrates about the boundaries of three separate squares which measure 2 cm, 4 cm, and 6 cm along each side. The corners of these squares are formed by locations 02, 22, and 00 for Graphs 1 through 3 (identical with Graphs 1 through 3 of Fig. 9), by locations 04, 44, 40, and 00 for Graphs 4 through 6, and by locations 06, 66, 60, and 00 for Graphs 7 through 9, respectively. Location 00 is common for all three of these squares. Lead field theory would indicate that lead (Ck) should have a progressively less uniform field when the squares possess 2 cm, 4 cm, and 6 cm sides along which the dipole migrates. This is confirmed in Fig. 10 by Graphs 1, 4, and 7, which show increasing voltage deflections and also by their respective cancellation coefficients: e.g., C_1 increases from 5.7 to 18 to 35 per cent for Graphs 1, 4, and 7, respectively.

R and r cancellations were computed using the 4 points (C, G, K, and O) and are illustrated in Fig. 10. As the uniformity of the field decreases, the R cancellations represented by Graphs 2, 5, and 8 respectively demonstrate increasing voltage deflections and increasing cancellation co-



Dipole Locations 02 at 12 12 at 24 22 at 36 21 at 48 20 at 60 10 at 72 00 at 84

Graph (1) R (C-K) $-(3.3X+2.92)C_1$ 7.4 C_2 57% C_3 0.3%
 (2) R (C-K) $-(4.6(4.0)K)+6.8(K)C_1$ 32% C_2 32.4 C_3 1%
 (3) R (256+256) (4.0+6.0) C_1 17% C_2 19% C_3 15% C_4 16%

[R-C K] (3.3X+2.92) C_1 8.2 C_2 8.2% C_3 0.4%
 [R-C K] (4.6(4.0)K) 6.8(K) C_1 34% C_2 35.4 C_3 8%
 [R-C K] (256+256) (4.0+6.0) C_1 4.4 C_2 27% C_3 20% C_4 100%

Dipole Locations 24 at 12 34 at 24 44 at 36 43 at 48 42 at 60 32 at 72 22 at 84

Graph (4) R (C-K) (5X+52) C_1 11% C_2 8.4 C_3 1%
 (5) R (C-K) 20(4.0+K) 6.8(K) C_1 38% C_2 34% C_3 1%
 (6) R (256+256) (4.0+6.0) C_1 5.8 C_2 20 C_3 20% C_4 20%

[R-C K] (5X+52) C_1 15% C_2 12% C_3 1.3%
 [R-C K] (20(4.0+K) 6.8(K) C_1 35.4 C_2 40% C_3 15%
 [R-C K] (256+256) (4.0+6.0) C_1 6.7% C_2 27% C_3 20%

Dipole Locations 46 at 12 46 at 24 66 at 36 65 at 48 64 at 60 64 at 72 44 at 84

Graph (7) R (C-K) (2X+12.72) C_1 18% C_2 18% C_3 3.3%
 (8) R (C-K) 35(4.0+K)+6.8(K) C_1 84% C_2 35% C_3 30%
 (9) R (100+100) (4.0+6.0) C_1 18% C_2 28% C_3 28% C_4 28%

[R-C K] (2X+12.72) C_1 19% C_2 18% C_3 3.7%
 [R-C K] 35(4.0+K)+6.8(K) C_1 84% C_2 35% C_3 37%
 [R-C K] (100+100) (4.0+6.0) C_1 18% C_2 30% C_3 28% C_4 28%

Fig. 9. Only the seven solid line vectors of Fig. 1 those occurring at 12 4 36 48 60 72 and 84 msec are considered. The successive dipole locations are placed at various positions on the transverse plane so that the dipole migrates about three different 2-cm squares. Graphs 1 through 3 are based on the dipole migrating about the more centrally placed 2-cm square formed by locations 0 12 24 21 20 10 and 00 at 12 24 36 48 60 72 and 84 msec respectively. Graphs 4 through 6 are based on the dipole migrating about the periphery placed 2-cm square formed by locations 46 56 66 65 64 54 and 44 at 12 24 36 48 60 72 and 84 msec respectively. Graphs 7 through 9 are based on the dipole migrating about an intermediate placed 2-cm square formed by locations 24 34 44 43 47 37 and 27 at 12 24 36 48 60 72 and 84 msec respectively. Graphs 1 4 and 7 representing R cancellations indicate that the field of lead (C-K) becomes less uniform as the 2-cm square assumes more peripheral locations. Graphs 2 5 and 8 display R cancellations and Graphs 3 6 and 9 display r cancellations. All of the graphs represent minimum range cancellations. Minimum root mean square calculations were also calculated but are not illustrated by graphs. The data from the root mean square calculations are given within the brackets for comparison with the corresponding data obtained from the corresponding minimum range computations.

efficients e.g. C_1 increases respectively from 32 to 79 to 99.8 per cent. The voltage deflections of the r cancellations show marked diminution in the case of the 4 cm square (Graph 6) as compared with the 2 cm square (Graph 3). The voltage deflections of the r cancellations with the 4 cm and 6 cm squares (Graphs 6 and 9 respectively) are approximately the same. The cancellation coefficients designated as c are similar for the 2 cm and 4 cm squares (13 and 15 per cent respectively) whereas this coefficient is lower for the 6 cm square (8.1 per cent). Cancellation coefficients c , c_1 and c_2 all increase for the 2 cm, 4 cm and 6 cm squares respectively.

In practice an R type of cancellation is usually carried out by combining 3 rather than 2 leads to cancel a fourth independent lead. The 3 leads are considered to be necessary because of the three dimensional character of the heart's electromotive forces. It was thought that it might be of interest to investigate how an extra degree of freedom may influence the cancellations obtained with a two dimensional model.

Accordingly the study illustrated in Fig. 10 is repeated when a third lead (H N) is combined with leads (O h) and (G h) to cancel lead (C h) in accordance with Equation (5R). The results are depicted in Fig. 11 (Graphs 1, 2 and 3 represent the minimum range R cancellations carried out when the dipole moves about the respective 2 cm, 4 cm and 6 cm sides of the three squares. These graphs should be compared respectively with Graphs 2, 5 and 8 of Fig. 10. It is noted that the contours of the cancellation deflections of Fig. 11 are markedly at variance with the corresponding graphs of Fig. 10. The cancellation coefficients of Fig. 11 are also smaller than the corresponding coefficients of Fig. 10. Moreover the contribution of lead (G h) is completely reversed (for both R and R') as shown by the uniformly negative values of q in Fig. 11. Despite the fact that leads (H N) and (C h) are anatomically perpendicular lead (H N) makes a greater contribution to the cancellation of lead (C h) than either lead (O h) or lead (G h). This is demonstrated in Fig. 11 by the fact that q_2 is numerically larger than either q_1 or q_3 for both R and

R. These results raise the possibility that cancellation studies involving three degrees of freedom may introduce a factor which lowers the cancellation coefficient fortuitously. This point will be considered in greater detail in the Discussion.

Discussion

An R type of cancellation can be obtained from the time varying voltages taken from the surface of a model (or from the body surface) without any knowledge of the nature of the internal generator. On the contrary the calculation of an R type of cancellation from Equation (R) requires that the mean orthogonal components (X , Y and Z) of the internally generated forces be known at each instant that a difference in potential is recorded with a surface lead. Thus an R' type of cancellation is not applicable to the study of the dipole property of the human heart. The terms x , y and z of Equation (R) represent the constant components of the unique vector which minimizes the series of R voltages. For convenience this vector will be referred to hereafter as the uniform lead field vector. In the application of Equation (R) three degrees of freedom are involved since x , y and z may all assume values which are independent of each other. In contrast the components x , y and z of the image vector of a dipole location are not independent but dependent on the dipole location with respect to the lead in question. If such an image vector were substituted for the uniform lead field vector Equation (R) would become

$$P = P - Q(Xx + Yy + Zz) \quad (R')$$

where the series of R voltages could be minimized by the optimal selection of the dipole location (fixing the values of x , y and z) and by the determination of the optimal value for the coefficient Q which remains constant at all instants of time. The minimized series of R deflections represents the nonfixed dipole content of lead I, that is the voltage deflection which could not be obtained with a single equivalent dipole at a fixed but optimal location for this particular lead. If the volume conductor is infinite a dipole location x_1 , y_1 and z_1 exists which permits (QXx) , (QYy) and (QZz) to be equivalent to (Xx)

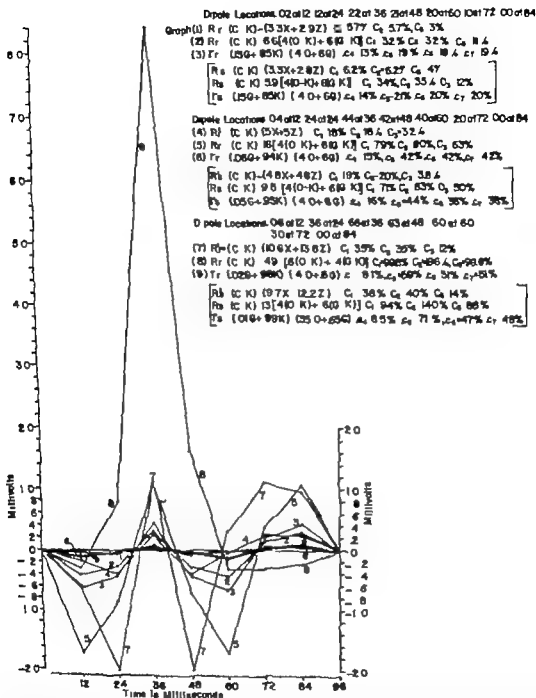
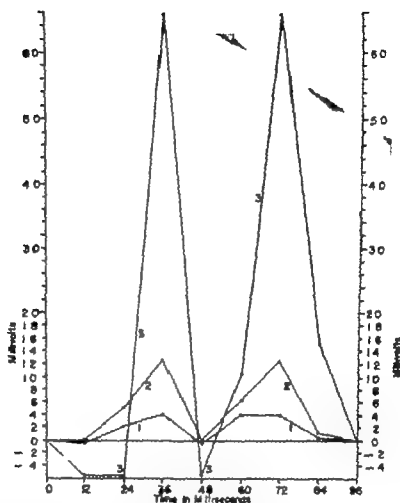


Fig. 10 As in Fig. 9 this illustration is also based on the same even solid line vectors of Fig. 1 (graphs 1 through 3) re based on the dipole migrating about a 2-cm square formed by location 0 1 7 21 70 10 and 00 13 24 36 11 60 7 and 81 sec respectively. (Graphs 1 through 3 of Figs. 9 and 10 are identical.) Graphs 4 through 6 are based on the dipole migrating about a 4-cm square formed by location 04 24 44 47 40 70 and 100 at 1 24 36 45 60 and 84 msec respectively. Graphs 7 through 9 are based on the dipole migrating about a 6-cm square formed by locations 06 36 66 63 30 and 00 at 17 24 36 48 60 72 and 81 msec respectively. Graphs 1 and 7 representing R cancellations indicate that the field of lead (C K) becomes less uniform as the square time a larger size. Graphs 5 and 8 represent I cancellations and Graphs 6 and 9 dipole cancellations. As in Fig. 9 only the minimum range cancellations are illustrated but data for maximum range cancellations are given within the brackets for comparison with the corresponding minimum range data.



Dipole Locations: 06 at 12, 36 at 24, 36 at 36, 36 at 48, 36 at 60, 36 at 72, 00 at 84
 Graph (1) R_z (C-K) $17(7780 \text{ N}) 7780\text{-K} + 1(\text{H-N})$ $C_1 30\% C_2 27\% C_3 4.2\%$
 $[R_z \text{ (C-K)} 12(710 \text{ K}) 5(0 \text{ K}) + 1(\text{H-N})] C_1 23\% C_2 23\% C_3 5.3\%$
 Dipole Locations: 04 at 12, 24 at 24, 44 at 36, 42 at 48, 40 at 60, 20 at 72, 00 at 84
 Graph (2) R_z (C-K) $25(710 \text{ K}) 75(0\text{-K}) + 1(05 \text{ H-N})$ $C_1 36\% C_2 36\% C_3 12\%$
 $[R_z \text{ (C-K)} 25(6640 \text{ K}) 64(0 \text{ N}) 38(\text{H-N})] C_1 46\% C_2 49\% C_3 21\%$
 Dipole Locations: 06 at 12, 36 at 24, 06 at 36, 63 at 48, 60 at 60, 30 at 72, 00 at 84
 Graph (3) R_z (C-K) $34(810 \text{ K}) 810 \text{ K} + \text{H-N}$ $C_1 82\% C_2 80\% C_3 67\%$
 $[R_z \text{ (C-K)} 40(810 \text{ K}) 4(0 \text{ K}) + 60(\text{H-N})] C_1 90\% C_2 127\% C_3 82\%$

Fig. 11 The dipole locations forming 2-cm, 4-cm, and 6-cm squares are identical to those of Fig. 10. Graphs 1, 2, and 3 correspond to Graphs 2, 5, and 8 respectively of Fig. 10. In addition to the two leads (O-K) and (G-K) used in Fig. 10 to form the lead which cancels lead (C-K), a third lead (H-N) is combined with leads (O-K) and (G-K) to form the cancelling lead. Although lead (H-N) is anatomically perpendicular to lead (C-K), it makes a contribution to the cancelling lead which is larger than that of either lead (O-K) or lead (G-K) in all three cancellation graphs. This produces a considerable discrepancy between the cancellation coefficients and the contours of Graphs 1, 2, and 3 of Fig. 11 and Graphs 2, 5, and 8 of Fig. 10 respectively.

($\chi y'$) and (Zx) respectively so that R'' and R are identical. This equality results from the fact that the selection of the spatial dipole location involves three degrees of freedom which are unrestricted in an infinite spatial medium. If the volume

conductor is finite its boundaries restrict such a selection. A dipole location with an image vector having precisely the same direction as the uniform lead field vector need not then exist in which case the minimized series of R' voltages obtained with

Equation (R') exceeds the minimized series of R' voltages obtained with Equation (R). In the present study in which the moving dipole of Models I and II generates no Y forces the (Q'_{yy}) term of Equation (R') is zero. If the transverse plane of Frank's model were infinite rather than bounded by the surface of the model as shown in the inserts of Figs. 3 and 4 the selection of a dipole location would involve two degrees of freedom without restriction and (Q'_{xx}) and (Q'_{zz}) of Equation (R') could be made equivalent to (λ_x^2) and (λ_z^2) respectively resulting in equality of R' and R. However as the result of the boundary of the transverse plane this equivalency would not always occur since the fixed location of the single equivalent dipole is postulated to be on the transverse plane. Consequently in the present report all of the graphs of minimized R' voltages represent the content of lead (Ck) which results from the nonuniformity of its lead field. The nonfixed dipole content of lead (Ck) could be either identical with or somewhat larger than that indicated by the R' voltages.

It is profitable to examine the studies of McFee and Parungao¹² in terms of the concept developed in the preceding paragraph. These authors utilized mathematical models consisting of either two or seven simultaneously functioning dipoles located in an infinite homogeneous medium. In the case of the model consisting of two dipoles these were separated by a distance of 6 arbitrary units and an exploring unipolar electrode was located 9 units from the closest dipole along the line determined by the sites of the two dipoles. This line was oriented at equal angular distances from the orthogonal reference axes. In the case of the model consisting of seven dipoles one was located centrally and the other six were arranged symmetrically so that each was located 4 arbitrary units from the central dipole yielding a maximum dipole separation of 8 units. This model was studied with two different unipolar electrode placements. In one instance the unipolar electrode was located 12 units from the central dipole and in the other instance it was placed 24 units from the central dipole. In both instances the axis formed by the central dipole and the unipolar elec-

trode was oriented at equal angular distances from the orthogonal reference axes.

The voltages of the unipolar electrode were cancelled by combinations of three leads referred to by the authors as x, y, and z heart vector leads oriented along the orthogonal reference axes. McFee and Parungao¹² state: "The voltages in the x, y, and z heart vector leads were proportional to the projection of the components of the electromotive forces in their direction and not dependent on the location of the electromotive forces." This statement implies that these voltages were calculated as though the image vectors for all the dipoles were orthogonal and of equal magnitude that is as though these leads possessed uniform lead fields. These authors¹² then state: "The voltage at the close exploring electrode did depend on the distance between this electrode and the various electromotive forces and proper allowance was made for this as well as for variations in the orientation of the different components of the different electromotive forces with regard to the exploring electrode." This statement implies that the voltages at the unipolar exploring electrode were calculated in accordance with the true magnitudes and orientations of the image vectors of the multiple dipoles. Consequently the cancellation graphs can be interpreted as representing the content of the unipolar exploratory lead resulting from the nonuniformity of its field and since the medium is infinite this is equivalent to the nonfixed dipole content of this lead. McFee and Parungao¹² report a total of eight cancellations calculated to yield a minimum peak rather than a minimum peak-to-nadir excursion of the voltage deflections. The cancellation coefficients calculated as the ratio of the peak deflection of the cancellation voltage to the peak deflection of the voltage of the unipolar lead were 16 and 14 per cent for the two dipole model, 10, 17, and 17 percent for the seven dipole model with the close exploring electrode and 7, 19, and 14 per cent for the seven dipole model with the more distant exploring electrode. McFee and Parungao did not consider that these relatively low coefficients expressed the nonfixed dipole content of the eight unipolar leads calculated from the multiple

dipole models. As an alternative they compared in the same instances the voltages produced at the exploring electrode by the two or seven dipoles with the voltages produced at the same electrode when the dipole sources of all of the electromotive forces were located at a single point at the centers of the models. Thus considered the discrepancy between the two graphs of these voltage deflections to represent the nonfixed dipole content or proximity potentials of the unipolar exploring electrode. It is the thesis of Melce and Parungio¹¹ that they have demonstrated that the voltages at a unipolar electrode in close proximity to a number of separate dipoles can contain substantial nonfixed dipole content and at the same time they can be efficiently cancelled by the voltages computed from a suitable combination of three orthogonal leads. It is our contention that their results do not support such a conclusion. As already pointed out their cancellation graphs calculated as minimum peak Π cancellations actually represent the nonfixed dipole content of the voltages at the unipolar exploring electrode. The superposition of the dipole sources of electromotive forces at a single central point is an unsatisfactory method of determining the minimum fixed single dipole content produced at the unipolar exploring electrode by the separate multiple dipoles. Such a central placement does not utilize the three degrees of freedom inherent in the selection of the optimal spatial location of an equivalent fixed dipole since the components x_1 and x_2 of the image vector of Equation (R) thus become arbitrary constants which are completely unrelated to the constraint components x_3 and x_4 of the uniform lead field vector of Equation (R'). Moreover the coefficient Q of equation (R) which provides an additional and entirely justifiable means of maximizing the fixed single dipole content of a multiple dipole generator is completely neglected. Finally, as the result of assuming uniform lead fields for their orthogonal leads the cancellation coefficients of Melce and Parungio¹¹ are much lower than would have been obtained had the voltages of these leads been computed with regard to the true magnitudes and orientations of the separate multiple dipoles. The basis for

this contention can be illustrated by Graphs 1 and 5 of Fig. 5 of this communication. Graph 1 represents the content of lead (C K) which results from the lack of uniformity of its field when the dipole migrates about the periphery of the 6 cm square. Graph 5 represents the cancellation of lead (C K) by the cancelling leads (O K) and (E K). If leads (O K) and (E K) had been assumed to possess uniform lead fields which is the assumption made by Melce and Parungio¹¹ in connection with their orthogonal cancelling leads Graph 5 would have been identical with Graph 1. Without this assumption the cancellation coefficient C_1 of Graph 5 is 94 per cent in contrast to the much lower value of 37 per cent for C_1 of Graph 1. The exceedingly poor degree of cancellation represented by Graph 5 can be explained by the fact that the two cancelling leads (O K) and (E K) form lead $12 [4 (O K) + 6 (E K)]$ the field of which diverges considerably from a uniform lead field. Thus in R cancellation calculated (but not illustrated) for lead $12 [4 (O K) + 6 (E K)]$ yields a value of 82 per cent for C_1 which exceeds by a considerable margin the corresponding coefficient of 37 per cent for the R cancellation of lead (C K) and indicates that the synthesized cancelling lead has much less uniformity of its field than that of the lead which it cancels.

If the location of the single dipole were stationary all of the cancellation coefficients listed in Figs. 5 through 11 would be zero. On the contrary, as the result of migration of the dipole, cancellation coefficients of considerable magnitude are frequently obtained. Cancellations of the R type involving connections with four points on the surface of the transverse section will be considered first. The magnitudes of the R voltages of such a cancellation depend largely on the positions of the electrodes of the cancelling leads with respect to the positions of the electrodes of the lead being cancelled. For example, in the inserts of Figs. 3 and 4, if point K is a common electrode site of all three leads and if the two remaining electrodes of the cancelling leads approach as a limit the location at point C of the remaining electrode of the lead being cancelled the resulting coefficients C_1 , C_2 , and C_3 will all approach zero as a limit. To

consider the other extreme if the two remaining electrodes of the cancelling leads approach a limit the location of the common electrode at point h , the cancellation coefficients C_1 and C_2 approach 100 per cent as a limit whereas C_3 approaches 200 per cent. C_1 and C_2 have similar numerical values when R is relatively small but C_2 grossly exceeds C_1 when R is relatively large. When R is quite large C_3 is only slightly lower than C_1 . However when R is relatively small C_3 is considerably lower than C_1 . Thus if C_1 is 10 per cent (in which case C_2 would have a similar value) C_3 is only 1 per cent. This fact accounts in a large part for the apparent excellence of the cancellation coefficients calculated as $(100/C_3)$ which Scher and his associates⁸ obtained with factor analysis.

The graphs of the R cancellations displayed in Fig. 5, 6, 9 and 10 have cancellation coefficients which do not serve as adequate estimates of the corresponding coefficients of the R cancellations. The R type of cancellation however can be utilized to determine the extent to which the deflections of an lead precordial or otherwise may be matched by the deflections of a lead derived from a vectorcardiographic reference system. This is of considerable practical importance in estimating the theoretical value of vectorcardiography. Okada, Langner and Briller⁹ used the x and z leads of Schmitt's SV EC III system¹⁰ for cancelling a lead formed by an anterior chest electrode and a mid back electrode placed at the same transverse level. They cancelled seven such leads with anterior chest electrodes located approximately at points A through G of the inserts in Figs. 3 or 4 on 19 normal individuals and on 6 patients with healed myocardial infarction obtaining averaged C_2 coefficients of 23 and 29 per cent in the former and latter groups respectively. These results exclude 1 additional normal subject and 2 additional patients with healed infarctions in whom C_2 values exceeding 60 per cent were obtained for two or more precordial sites. Okada and his associates carefully and rightfully point out that a cancellation coefficient gives the percentage of chest lead potential which is not recorded by the lead system in ques-

tion and does not necessarily reflect the nonfixed dipole content of the chest lead since it is not valid to assume that the vectorcardiographic leads have completely uniform fields. Their use of only the x and z leads of the SV EC III system represented a conservative approach since they realized that the chest leads being cancelled were located approximately on the transverse or xz plane and would therefore possess only small y components. They compensated for such minimal y components by carrying out an apparently limited vertical search with the anterior chest electrode. If they had utilized all three leads of the SV EC III system a spuriously low cancellation coefficient would have resulted whenever the y lead formed a major proportion of the three cancelling leads. Examples of spurious cancellations are illustrated in Fig. 11 of this paper in which it is demonstrated that the introduction of a third cancelling lead into a basically two dimensional situation may drastically change the configuration of the graph of the residual voltages and sometimes strikingly reduce the cancellation coefficient.

In another study published in abstract form Briller and Okada¹¹ described the results of three dimensional cancellations in which Precordial Leads V_1 through V_4 were each cancelled by a combination of three leads formed by the potentials of the right arm, left arm and left leg, measured against the potential of an electrode on the back. They report mean cancellation coefficients (apparently C_1 values) which vary in the normal individuals from a maximum of 19 per cent for Lead V_1 to a minimum of 13 per cent for Leads V_3 and V_4 and in cardiac patients from a maximum of 38 per cent in Leads V_3 and V_4 to a minimum of 28 per cent in Lead V_1 . In this study the maximum efficiency of the tetrahedral reference frame¹² in synthesizing precordial leads is presented. Since none of the three cancelling leads lie on the plane of the precordial leads being cancelled the use of the three dimensional technique may be justified. It should be realized however that such cancellations may involve spurious combinations of the three cancelling leads so that the lead fields of the synthetic leads and of the precordial leads may be considerably at variance.

Cancellations of the r type will be considered next. In the present study the m and n coefficients of Equations 1r, 2r, 3r, and 4r are varied and the points on Frank's transverse plane designated by the various capitalized letters in these equations remain constant in location. This technique which involves only two degrees of freedom differs from that used by investigators who have reported cancellations of this general type performed on individuals with either normal or abnormal hearts.¹⁷ In all of these studies one electrode designated as the search electrode is moved in an unlimited manner from one location to another over the surface of the body. Only one of the coefficients either m or n depending upon which modified the potential of the search electrode is varied. Such techniques involve three degrees of freedom since movement of the search electrode over the two dimensional surface of the body involves two degrees of freedom and the variation of one of the coefficients provides a third degree of freedom. It was noted that the graphs of r cancellation patterns illustrated in Figs. 7 through 10 show relatively small deflections. It is obvious that the addition of one more degree of freedom would further reduce the magnitude of these deflections.

As demonstrated in Figs. 9 and 10 the deflections of an r cancellation may decrease when a moving dipole migrates through a longer distance or is allowed to approach more closely a precordial electrode. Such paradoxical findings may be emphasized or reversed by the methods used to calculate coefficients for expressing the cancellations numerically. Thus the coefficient c_1 may decrease as the nonfixed dipole content of the model increases. Since c_1 was utilized by Frank in his interpretation of multiple cancellations of the r type obtained from a single normal individual his conclusion that the QRS complex recorded from any point on the body surface of his subject could be accounted for by an equivalent fixed dipole with an accuracy of about 5 per cent is unwarranted. Although the coefficients c_2 , c_3 , and c_4 increase as the nonfixed dipole content of the model increases study of Figs. 9 and 10 indicates that there are no direct or predictable relationships between the

graphs of R and those of r and that neither c_2 , c_3 nor c_4 yields any reliable information concerning the nonfixed dipole content of either of the models. Therefore there is no justification for the contention of those investigators¹⁷ who suggested that the accuracy of the single equivalent dipole representation of the heart could be quantitatively predicted from the c_1 coefficient calculated from the cancellation of mirror patterns of normal and abnormal QRS complexes. On the other hand Brody and his co-workers^{18,19} who utilized c_1 and c_2 in their studies pointed out that cancellation techniques provide little detailed information concerning deviation of cardiac behavior from an equivalent fixed location dipole. They cancelled both esophageal and right arm potentials with the potentials of a variably located precordial electrode employing a four electrode technique of the r type. They suggested that such a cancellation results in a null lead which is relatively insensitive to the electromotive forces of the heart despite its proximity to the esophageal and/or precordial electrodes. They also pointed out that deflections at any two instants during the cardiac cycle can always be completely cancelled and therefore that complete cancellation of the maximum positive deflection and maximum negative deflection of any lead is assured a priori. It is profitable to examine this latter concept from a mathematical standpoint as well as in the light of the results obtained in the present study. If n leads are used to form the cancelling lead of a minimum range cancellation the upper (positive) limit of the cancellation graph may be formed by 1 to $(n+1)$ points and if there is more than one such point all have the same potential. If the number of points forming the upper limit is m the number of points forming the lower (negative) limit of the graph is $(n+2) - m$ again if there is more than one such point all have the same potential. If the cancellation graph does not cross the zero (isoelectric) line either the positive or the negative limit of the graph is formed by 1 to $(n+1)$ points and if this quantity m exceeds one will have the same potential. There are then $(n+1) - m$ potentials which are completely cancelled and are distributed as points along the zero line in addition to

the two zero end points. These zero end points collectively may be considered to represent an additional single limiting point so that the number of points forming one limit of the graph at the zero line is actually $(n + 2) - m$ with the other limit being formed by 1 to $(n + 1)$ points thus the special case in which the cancellation graph does not cross the zero line has in reality the same number of upper and lower limiting points as the cancellation graph which crosses this isoelectric line one or more times (which may be as many as one less than the number of potential points between the zero end points). Except for those instances in which critical points limiting a minimum range cancellation are located on the zero line other potential points lying between the positive and negative limiting points do not have a zero value unless this occurs fortuitously. Therefore the complete cancellation of the maximum positive deflection and the maximum negative deflection of a lead does not result in a minimum range cancellation.

Fig 11 illustrates minimum range R cancellations in which the number of leads n forming the cancelling lead is 3. The total number of critical limiting points is therefore $(n + 2)$ or 5. Graph 1 demonstrates 3 positive points with equal potential and 2 negative points with equal potential. In the case of Graph 2 there are 2 equal positive points and 2 points on the zero line between the zero end points which can be considered to represent a third zero point. Graph 3 is limited by 2 equal positive points and 3 equal negative points. In Figs 9 and 10 the R cancellations are produced by two cancelling leads so that the number of limiting potential points is $(n + 2)$ or 4. Likewise in r cancellation also has 4 limiting points since it is derived by rearrangement of terms from an R cancellation formed by two cancelling leads. In the case of a two dimensional situation an R cancellation also has 4 limiting points since it can be considered to be analogous to an R cancellation formed by two cancelling leads. In Figs 9 and 10 all of the minimum range R, R and r cancellations are limited

by 2 positive points with equal potential and 2 negative points with equal potential with the exception of Graph 8 of Fig 10 which is limited by a single positive point and 3 equal negative points. Since the same number of critical limiting points and the same number of degrees of freedom are involved in achieving optimum R and r cancellations it is apparent that the great difference in the magnitude of the range of the respective R and r graphs cannot be explained on the basis of these factors. Rather the differences between R and r graphs are dependent upon the differences in the lead fields of these two types of cancellation leads. We agree with Brody and his associates^{4,7} that the lead field of an r cancellation is essentially that of a null lead which records inherently low voltages.

Summary and conclusions

The cancellation of an actual lead by a synthetic lead formed by combining two or three other leads cannot serve as an adequate index of the extent to which the heart can be represented by a single fixed location dipole. Such a cancellation depends partially on the proximity of the electrode or electrodes of the actual lead to the electrodes of the leads forming the synthetic lead. This type of cancellation (referred to in this communication as an R cancellation) can be used to determine the extent to which the deflections of any lead precordial or otherwise can be matched by the deflections of a lead synthesized from two or three orthogonal leads of a vectorcardiographic reference system. If all of the leads of such a system are applied in the formation of the synthetic cancelling lead considerable care must be exercised in the interpretation of the cancellation pattern. A spuriously low cancellation coefficient may be obtained if one vectorcardiographic lead contributes substantially to the formation of the synthetic lead when the lead being cancelled lies largely on the plane formed by the other two vectorcardiographic leads.

An R cancellation is best evaluated quantitatively by the ratio in per cent of the magnitude of the cancellation residual to the magnitude of the cancelled lead. Less satisfactory is the ratio in per cent of the magnitude of the cancellation residual to

*The more or less descriptive of minimum range cancellation graph which does not cross the zero line that which was given in the previous publication.¹¹

the mean of the magnitudes of the cancelled lead and the synthesized cancelling lead this ratio exceeds 100 per cent when the cancellation residual is relatively large. The square of the ratio of the magnitude of the cancellation residual to the magnitude of the cancelled lead greatly overemphasizes the apparent excellence of any cancellation having a relatively small residual. This partially explains the inordinately good cancellation coefficients (99 per cent or higher) reported by investigators⁹ who in effect subtracted this squared ratio from one and expressed the result in per cent by multiplying it by 100.

Mirror image cancellations (referred to in this communication as *r* cancellations) produce inherently low voltages so that their deflections are considerably smaller than those of *R* cancellations obtained with electrodes at identical locations. An *r* cancellation does not yield any reliable information concerning the accuracy of representing the heart as a single fixed location dipole. In fact our studies indicate that the deflections of an *r* cancellation sometimes diminish with an increase in the distance traversed by a single moving dipole. Moreover some of the cancellation coefficients which have been applied to *r* cancellations may vary inversely with the magnitude of the deflections of the cancellation graph. Consequently several published estimates of the percentage of non-dipolar activity of the heart based on mirror image cancellations cannot be accepted as valid.

In the case of a model *r* cancellation technique referred to herein as an *R* cancellation can be used to demonstrate the minimized residual voltages of a lead resulting from nonuniformity of its lead field. If the model's conducting medium is infinite the nonfixed dipole content of the lead based on the optimal location of a postulated single dipole is identical with that resulting from lack of lead field uniformity. If the model's medium is bounded rather than infinite these two quantities may or may not be identical; the nonfixed dipole content may be somewhat larger but can never be smaller. Utilizing models of multiple dipoles within an infinite medium McFee and Parungao published cancellation graphs which were actually *R*

cancellations. McFee and Parungao did not consider that their cancellation graphs represented the nondipolar contents of their leads; for these estimates they used another computational technique which *a priori* would be expected to produce larger residuals than the minimized residuals of the *R* cancellations. Their data do not justify their conclusion that the voltages at a unipolar electrode in close proximity to a number of separate dipoles can contain substantial nonfixed dipole content and at the same time can be efficiently cancelled by voltages formed by a suitable combination of orthogonal leads. If the voltages of their orthogonal leads had been dependent upon not only the magnitudes and orientations but also the locations of the separate dipoles they would have computed *R* rather than *r* cancellations. Cancellation coefficients of the *R* type were always substantially larger than those of the *r* type in our own studies except in one instance (exemplified by Graph 1 and 1 of Fig. 6) which resulted from proximity of the precordial electrodes of the cancelling leads with the precordial electrode of the lead being cancelled. This condition would not have obtained in any of the experiments of McFee and Parungao. Had they calculated *R* cancellations as well as *r* cancellations they would have found that the former representing the type of cancellation which can be performed experimentally on human subjects would have been substantially larger than the *r* cancellations which they illustrate. Since an *R* cancellation represents the nonfixed dipole content of the cancelled lead when the medium is infinite their studies would then have agreed with our conclusion that an *R* cancellation usually grossly overestimates rather than underestimates the degree of nondipolarity of a lead.

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Present status of the concept of oxygen differential in the etiology of ventricular fibrillation after coronary occlusion

Henry S. Badeer M.D.*

Brooklyn N. Y.

In a recent symposium on Sudden Cardiac Death held at the University of Kentucky Medical Center the view was expressed that the role of oxygen differential in the pathogenesis of ventricular fibrillation (VF) after coronary occlusion is a subject of controversy.¹ At the same symposium in reply to a query on Beck's concept of oxygen differential Harris² stated that in acute coronary occlusion ventricular ectopic beats (hence VF) which are said to arise at the boundary between oxygenated and nonoxygenated cardiac tissue are due to the outpouring of potassium from the ischemic muscle cells. In his opinion local potassium diffusion gradients were essential for the production of ventricular arrhythmias soon after coronary artery occlusion.

The purpose of this communication is to outline briefly the concept of oxygen differential as proposed by Brofman, Leightner, and Beck³ in 1956 and to present the experimental data that have accumulated since then for or against the hypothesis. Although I have reviewed the pathogenesis of VF soon after coronary occlusion in a recent article⁴ I think that a more detailed discussion of the concept of oxygen differential is warranted because of its wide acceptance and also because

of the fact that additional data have accrued since the above mentioned review was written. It must be made clear that this analysis will be limited to VF that supervenes soon after experimental coronary occlusion (within 1 hour in dogs). It will not deal with the mechanism of delayed arrhythmias (ventricular ectopic beats or ventricular tachycardia) that develop 4 to 8 hours after a two stage coronary artery ligation in dogs persist for 2 to 4 days and then disappear spontaneously.⁵

For the details of the concept of oxygen differential the reader is advised to consult Beck's paper.³ In brief it stated that ventricular ectopic activity (hence VF) originates from currents that are set up between ischemic and well perfused regions of the ventricular myocardium because of the marked difference in the oxygen tension (concentration) that follows rapidly the occlusion of a major coronary artery. Impulses are believed to arise at the boundary zones. The size of the vessel (hence the mass of ischemic muscle) is important in reaching the threshold intensity of current that causes ectopic activity and fibrillation. It is also implicit in the concept that the greater the oxygen differential the greater will be the intensity

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*Present Professor, Department of Physiology, State U. of New York, Downstate Medical Center, 450 Clark Street, Brooklyn, N. Y. 11203.

of the current and the likelihood of reaching the fibrillation threshold. The essential observation that led to this hypothesis was that in contrast to coronary occlusion, acute fatal hypoxic hypoxia or asphyxia in the dog practically never caused VF. The heart became diffusely cyanotic, dilated and within a short period stopped beating (asystole).¹¹ Absence of fibrillation was attributed to the uniformity of anoxia in the myocardium. Although this observation has been repeatedly confirmed by others, it has been contradicted by Coffman and Gregg,⁷ who reported terminal VF in some dogs (particularly large size dogs) killed by asphyxia. On careful analysis it may be noted that VF in Gregg's experiments was detected only by electrocardiography and that it occurred about 15 minutes after blood pressure dropped to near zero. This is not comparable to the VF that follows coronary occlusion in which ectopic activity and VF occur when the heart is still pumping fairly adequately. A similar argument has also been advanced by Beck.⁴ The absence of VF has been noted also in acute fatal hemorrhage.⁴ Here too marked oxygen differentials are lacking. Coronary blood flow declines gradually throughout the entire myocardium and cardiac anoxia is diffuse.

Another interesting observation of Beck in support of his concept is that in an asphyxiated animal in which the heart is still beating, perfusion of one of the major coronary arteries with oxygenated blood may induce VF (so-called reverse trigger).⁴

Many workers including Beck have presented electrographic data to indicate differences in potential between ischemic and well perfused areas of the myocardium. However, there is no evidence that these currents originate from the differential in oxygen. In fact, Warren, Saurbrey and Wandall¹² have shown that the injury currents develop in the absence of significant differences in oxygen content between occluded and nonoccluded areas. In my opinion, the view that oxygen differential is responsible for these currents appears to be the weakest argument in the hypothesis of Beck. Besides, it is not certain that these differences in potential set up pacemaker activity in the ventricles.

In 1959, Badeer and Horvath¹³ attempted to test the hypothesis of Beck by other means. It was thought that if the concept of oxygen differential is correct, arrest of the entire coronary arterial blood flow to the myocardium should not induce VF but stop the heart in asystole. This procedure in dogs almost invariably led to VF soon after occlusion. On the basis of this, serious doubts may be raised about the importance of large differentials in the myocardium, not only in oxygen concentration and electrical potential but also in potassium concentration as postulated by Harris.¹⁴ However, it does not rule out the possible role of the release of potassium from ischemic cells in the initiation of ectopic activity.

In 1962, Danesi¹⁵ approached the problem in another way. He perfused the circumflex branch of the left coronary artery in dogs with homologous serum for a period of 1 hour and noted that in none of the 10 dogs did VF occur, whereas in a control series, occlusion of the circumflex artery caused VF in 60 per cent of the dogs. It was assumed in these experiments that perfusion of the circumflex artery with serum created a large oxygen differential between the serum and blood perfused regions of the myocardium. In line with these findings are the observations of Petropoulos¹⁶ who perfused in dogs the anterior descending coronary artery with mixed venous blood obtained from the right atrium of donor dogs (oxygen content = 13 volumes per cent) for a period of 30 minutes and followed this by 11 per cent dextran in saline for another 30 minutes. He observed no fibrillation in 10 experiments.

In 1962, I used still another method to test Beck's hypothesis.¹⁴ It was reasoned that in coronary occlusion the oxygen differential could be increased by the inhalation of 100 per cent oxygen and if the concept of oxygen differential is correct, this procedure should favor ectopic activity and VF. In 25 experiments on anesthetized open-chest dogs, it was found that the incidence of VF within a period of 1 hour after ligation of the anterior descending coronary artery in animals breathing 100 per cent oxygen was 28 per cent, whereas in a series of 25 control dogs

breathing room air the incidence was 20 per cent. The difference was not statistically significant. In this study the oxygen differentials were not measured but Siven and associates¹⁴ have shown by the polarographic method that inhalation of 100 per cent oxygen increased the pO_2 by 50 to 200 per cent or more in perfused regions of the ventricular myocardium whereas in ischemic areas there was hardly any rise at all. These experiments were significant not only in testing Beck's hypothesis but also in evaluating the possible hazards of administering oxygen to patients with acute myocardial infarction.

The investigations of Warren and co-workers⁹ showed that the pattern of injury is recorded by the epicardial electrogram as unrelated to the oxygen differential between ischemic and nonischemic areas. This was demonstrated by producing generalized hypoxia (inhalation of 4 per cent oxygen) and simultaneously occluding a coronary artery or releasing the occlusion during hypoxia. From these studies they concluded that the difference in oxygen concentration of ischemic and nonischemic areas of the myocardium was not responsible for the current of injury and VF in experimental coronary occlusion in the dog.

In this connection reference should be made to the observations of Jacobson, Schreus, and Moe.¹ These investigators noted that exposure to concentrations of oxygen between 5 and 10 per cent in the inspired air in unanesthetized dogs exhibiting delayed ventricular tachycardia (1 to 3 days after a two-stage coronary occlusion) reduced the frequency of discharge of the ectopic ventricular focus. At first sight this may be taken to support the concept of oxygen differential but a closer analysis shows that Moe's studies were concerned with delayed ventricular tachycardia which rarely terminates in VF whereas Beck's concept pertains specifically to early ventricular ectopic activity (within 1 hour after occlusion in dogs) which often terminates in VF. In the former case necrosis of tissue with microscopic changes is a prominent feature whereas in the latter the changes are essentially electrochemical with no microscopically detectable alterations. Furthermore hypoxic

hypoxia alters so much of cell physiology that the reduction in arrhythmia may be related not necessarily to the decline in oxygen differential per se but to almost any of the metabolic changes that occur.

Finally the experimental data of Char-dack and associates¹⁵ may be significant with respect to the concept of oxygen differential. These workers reported that a progressive increase in the pO_2 of the inspired air by the inhalation of 100 per cent oxygen at 1 atmosphere, 2 atmospheres and 4 atmospheres (absolute) tended to reduce the incidence of VF in anesthetized dogs in which the circumflex coronary artery was ligated. More striking beneficial results were reported by Smith and Lawson^{16,17} in dogs subjected to 100 per cent oxygen at 2 atmospheres (absolute) pressure. According to Beck's concept one expects that the markedly increased oxygen differential would increase the incidence of VF. On the contrary if anything it tends to decrease it. The situation is somewhat complex because although the oxygen differential and oxygen gradient are markedly increased the mass of ischemic tissue may be diminished under these circumstances by an improvement in the oxygen available to the tissue at the boundary. Since the mass of ischemic tissue plays a role in attaining the threshold value for ectopic activity and VF this may be the basis for the beneficial tendency of hyperbaric oxygen.

In summary it may be stated that all of the results of experimental studies carried out since the concept of oxygen differential was proposed in 1936 speak against the importance of oxygen differentials in the etiology of VF soon after acute coronary artery occlusion. The pathogenesis of ventricular fibrillation after coronary occlusion remains uncertain and the reader may benefit from a recent review on the subject.¹ Analysis of experimental data available to date suggests that the mechanism may involve a disturbance in myocardial cell metabolism and membrane properties related not so much to a lack of oxygen but rather to the arrest of flow of plasma (absence of perfusion) to a large mass of contracting myocardium. Whether it is the absence of

a substance(s) brought by the plasma or it is the removal of a metabolic product(s) by the plasma or both is unknown. It seems to be more likely that ectopic activity is related to an excessive accumulation of a metabolic product(s) that alters membrane properties. The absence of ventricular arrhythmias and VF in acute fatal hypoxic hypoxia, asphyxia or hemorrhage may be a question of the degree of accumulation (hence the concentration) of such a product(s) since in all of these conditions the coronary blood flow persists (although progressively curtailed) until all electrical activity of the myocardium ceases. This flow may wash away the metabolic products and reduce their concentration below threshold levels. Ischemic nonischemic boundaries in the ventricles do not seem to be essential for ectopic activity.

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The effects of morphine on the resistance and capacitance vessels of the peripheral circulation

*R. Peter Henney M.D.**

John S. Lesko M.D.

Robert K. Braaley M.D.

H. Neiland Oldham M.D.

Andrew G. Morrow M.D.

Bethesda Md.

Since its isolation and description over a century ago morphine has remained one of the most valuable drugs available to the physician. Morphine is commonly administered to patients with acute cardiovascular disorders such as shock, pulmonary edema or myocardial infarction and it is surprising that so little meaningful information is available concerning its effects on the heart and circulation. Many studies of the pharmacologic actions of morphine on the peripheral vascular system have been reported and although the results of these studies are conflicting the majority indicate that morphine has some dilating effect on peripheral vessels. In most investigations however no attempt was made to separate the cardiac effects of the drug from its peripheral ones and the depressed respiration of the morphinized animal was usually not taken into account.¹⁻⁵

Previous explanations of the effects of morphine on the vascular system were largely based upon classic concepts of the mechanisms of regulation of the peripheral

circulation and these in turn were largely concerned with the function of resistance vessels. It is now appreciated however that 60 to 80 per cent of the circulating blood volume is contained within the peripheral venous system and that this vascular bed is highly reactive and able to alter its capacity in response to a wide variety of physiologic and pharmacologic stimuli. In the capacitance vessels large changes in volume are associated with relatively small alterations in pressure and valid measurements of capacitance are possible only when the effects of cardiac contraction and respiration on venous pressure are eliminated. In this laboratory the effects of morphine on ventricular performance were assessed in intact dogs in which the heart was separated from the peripheral circulation by appropriate cardiopulmonary bypass techniques.⁶ Similar methods were employed in the present experiments concerning the effects of morphine on the resistance and capacitance vessels of the peripheral circulation.

* in the Clinic of Anesth. & Genl. Heart Institute, Bethesda, Md.

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Address: Clinic of Surgery, General Heart Institute, National Institutes of Health, Bethesda, Md. 20894.

Methods

Mongrel dogs ranging in weight from 18 to 30 kilograms were anesthetized with intravenous chloralose (60 mg per kilogram) and ventilated through a cuffed endotracheal tube with a volume controlled piston respirator supplying room air. A bilateral transverse thoracotomy was performed and heparin (3 mg per kilogram) was administered intravenously. Systemic arterial and central venous pressures were measured through polyethylene catheters inserted into the abdominal aorta and vena cava from the femoral artery and vein respectively. The catheters were connected to Statham p23Db transducers which were calibrated before each experiment with a water manometer. The zero or base line reference for all pressures was the level of the right atrium and recordings were made with a photographic or direct writing ocallograph. Body temperature was moni-

tored with an esophageal thermistor and was maintained at 36 to 37.5°C with a heat exchanger when cardiopulmonary bypass was employed. The pH of arterial blood was measured frequently during each experiment and remained between 7.35 and 7.45 in all animals.

The experimental methods utilized to assess changes in vascular resistance and capacitance were similar to those used by Ross and associates¹ in studies of the digitalis glycosides. The extracorporeal circuit was primed with a 2:1 mixture of Ringer's lactate solution and dextran; the priming volume was similar to the estimated blood volume of each animal and during bypass approximately 50 per cent hemodilution resulted. No homologous blood was administered since in the dog it is a well recognized cause of venous pooling.² All venous blood was drained from the right heart directly into a rotating disc

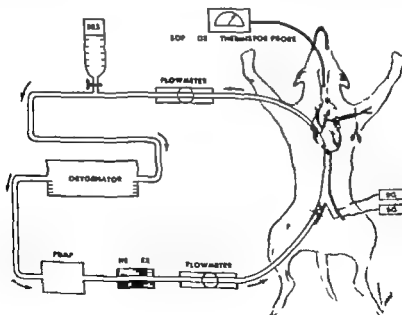


Fig. 1. Schematic representation of the cardiopulmonary bypass circuit utilized in the determinations of total peripheral arterial resistance and the capacity of the peripheral vascular compartment. In all experiments system blood flow was maintained constant and was constantly monitored by an electromagnetic flow meter in the arterial return line. Venous blood was returned from the right atrium (R1) and right ventricle (R2) to the pulmonary artery (P4) was occluded. Blood was returned from the oxygenator to the femoral artery (F1). Pressures were measured by means of pressure transducers (SG) attached to catheters inserted through the femoral artery and femoral vein (F1). The determinations of capacitance (venous return was also measured by a flowmeter in the venous return line and changes in blood volume were determined by the volume which was withdrawn from the calibrated reservoir (RES) to restore the blood level in the oxygenator to the control

oxygenator and arterialized blood was returned to the femoral artery at a constant rate through a calibrated totally occlusive pump (Fig. 1). The transducer of an electromagnetic flowmeter (Statham E 3000) was inserted into the arterial return line and systemic arterial flow was constantly monitored. Flow rates ranged from 58 to 91 ml per kilogram per minute and averaged 76 ml per kilogram per minute. After the institution of cardiopulmonary bypass a short period of circulatory stabilization was allowed and control measurements were then made. Morphine (1 mg per kilogram) was rapidly injected into the blood passing through the oxygenator and continuous observations were made during the subsequent 30 minute period.

Effects of morphine on resistance vessels

Thirteen dogs were studied during total cardiopulmonary bypass. Systemic arterial pressure and central venous pressure were recorded before and continuously for 30 minutes after the administration of morphine while systemic arterial flow remained constant. Total peripheral vascular resistance (TPR) was calculated from the following formula and expressed in dynes cm^{-2} :

$$\text{TPR} = \frac{(\text{MAP} - \text{MCVP}) \times 980}{\text{Flow}}$$

Where MAP = mean arterial pressure $\text{cm H}_2\text{O}$; MCVP = mean central venous pressure $\text{cm H}_2\text{O}$; Flow = systemic arterial flow ml sec^{-1} and 980 = conversion factor from $\text{cm H}_2\text{O}$ to dynes cm^{-2} .

In 3 additional dogs heparin was administered and two cannulae were introduced into the left common femoral artery, one directed proximally into the aorta and the other distally for 1 to 2 cm. Both cannulae were introduced into the artery through a single longitudinal incision; the artery was not divided. Arterial flow into the femoral artery was then controlled by an occlusive finger pump which perfused the distal artery with blood from the aorta. Arterial pressure was recorded from a small distal branch of the left femoral artery and central aortic pressure was simultaneously measured from a catheter inserted from the right femoral artery. The flow into the left femoral artery was adjusted

until the mean femoral arterial pressure was identical to the mean aortic pressure. Morphine (0.5 mg per kilogram) was rapidly injected into the perfused left common femoral artery as the pressures were continuously recorded.

Effects of morphine on capacitance vessels

The extracorporeal system previously described (Fig. 1) was utilized with certain modifications for assessment of the effects of morphine on the volume of the total systemic vascular compartment. In 12 dogs total bypass was instituted and after the stabilization period 300 to 500 ml of the completely mixed blood and priming solution were withdrawn from the circuit into a calibrated reservoir. The blood level in the oxygenator was then recorded and morphine (1 mg per kilogram) was rapidly injected into the blood within the oxygenator. An increased vascular capacity was reflected in a fall in the blood level in the oxygenator and this volume was measured as it was replaced from the reservoir. In 2 of the 12 dogs portal venous pressure was also recorded from a catheter inserted into the portal vein at prior laparotomy. Changes in blood volume were recorded over a 30 minute period. In 3 additional animals an intravascular flow transducer (Medicon QH 2100 c) was inserted into the line returning venous blood to the oxygenator and the instantaneous changes in venous return were recorded after the administration of morphine.

Venous tone was determined in 8 animals by the major vessel occlusion technique described by Bartelstone.¹⁰ After bilateral thoracotomy the azygos and highest intercostal veins and both internal mammary arteries and veins were ligated. The circulation to the lower half of the body was isolated by simultaneous occlusion of the inferior vena cava and descending thoracic aorta immediately above the diaphragm. Venous tone was expressed in $\text{cm H}_2\text{O}$ as the difference between control pressure in the inferior vena cava and the pressure recorded 30 seconds after the occlusion. Determinations of venous tone were made before and at intervals of 5 to 15 minutes after the intravenous injection of morphine (0.5 mg per kilogram). In these experiments the drug was administered slowly over a period of 30 seconds and

only modest changes in systemic arterial pressure resulted

Results

Effects of morphine on resistance vessels

1. In each of the 13 dogs studied during cardiopulmonary bypass total peripheral vascular resistance decreased after the administration of morphine (Table 1). In this experimental preparation arterial flow was constant and the systemic arterial pressure varied directly as peripheral resistance. A precipitous fall in systemic pressure occurred 30 to 90 seconds after injection of the drug and the pressure was lowest 3 to 5 minutes after injection the time at which the data in Table 1 were recorded. The total peripheral vascular resistance in the control period varied among individual animals (1 400 to 6 200 dynes sec cm^2) but was always lower after morphine. The maximum decreases in resistance ranged from 11 to 79 per cent of control values and the average decrease was 46 ± 20 per cent (± 1 S D). The reduced pressure (resistance) persisted for 5 to 6 minutes after which time the pressure gradually rose and approximated the control level 20 minutes after the injection (Fig. 2). In all dogs the pressure had re-

turned to the initial level by 30 minutes and in 7 animals it was higher than the control value at this time.

B The changes in pressure recorded in the perfused femoral artery and the aorta after the injection of morphine into the femoral artery were similar in each of the 3 animals and representative records from one experiment are reproduced in Fig 3. After the injection the pressures in both the femoral artery and the aorta remained unchanged for 20 to 30 seconds then fell simultaneously. The fall in femoral arterial pressure did not occur immediately but only after a delay during which it was possible for the injected drug to reach the central circulation. These observations indicate that morphine had no direct effect on resistance in the vascular bed supplied by the femoral artery.

Effects of morphine on capacitance vessels

A Significant increase in the capacity of the total systemic vascular compartment were noted in each of 12 dogs after the administration of morphine. The volume of blood in the oxygenator rapidly decreased 45 to 90 seconds after injection of the drug reflecting increases in the total blood volumes of the animals. The increases in blood volume ranged from 4.5 to 26 ml

Table 1 Total peripheral vascular resistance before and 5 minutes after administration of morphine (10 mg/kg)

1 in 1 number and 11 right (A.g.)	Systemic arterial flow (ml/min)	Mean arterial pressure (cm H ₂ O)		Mean venous pressure (cm H ₂ O)		Total peripheral vascular resistance (dynes sec cm ⁻⁵)		Change in total peripheral vascular resistance
		Before morphine	After morphine	Before morphine	After morphine	Before morphine	After morphine	
1 (71)	1 450	125	100	4	4	4 900	3 808	-21
2 (20)	1 580	65	55	4	3	2 270	1 940	-15
3 (25)	2 000	165	65	4	2	4 740	1 860	-61
4 (2)	2 000	100	55	7	3	2 740	940	66
5 (26)	1 900	95	50	4	3	2 870	1 450	-48
6 (19)	1 570	90	55	3	8	3 30	1 870	-46
7 (1)	1 620	40	30	2	1	1 250	370	-6
8 (30)	2 200	100	50	5	5	2 340	1 200	-33
9 (18)	1 500	90	55	1	0	3 490	2 160	-35
10 (23)	1 450	115	130	4	4	4 60	4 20	-11
11 ()	1 870	115	80	1	1	4 140	3 560	-41
1 (14)	1 050	115	25	8		6 210	1 790	-9
13 (22)	1 500	8	45	3	3	2 770	1 60	-37
						Mean ± 1 S.D.		-46 ± 20

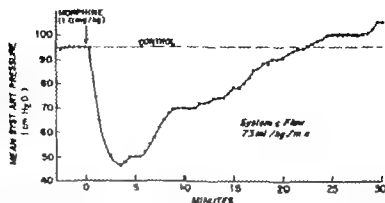


Fig. 2 Representative effects of morphine (10 mg/kg) on total peripheral vascular resistance in one animal. Since the total systemic blood flow was maintained constant, resistance varied directly as the mean systemic arterial pressure. Pressure (resistance) fell immediately after morphine was given, and the effect was most pronounced after 3 to 4 minutes. Thereafter the pressure gradually rose, approximated the control value at 20 minutes, and exceeded it at the end of the 30-minute period of observation.

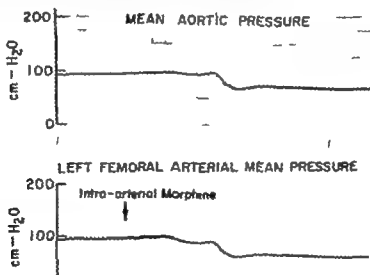


Fig. 3 Records of mean pressure recorded in the central aorta and in the perfused left femoral artery before and after the intra-arterial injection of morphine into the perfused vascular bed. The fall in pressure in the femoral artery occurred simultaneously with that in the aorta, indicating that morphine had no direct effect on resistance but acted on the perfused bed only after it had reached the central circulation and caused a general fall in resistance, as reflected in the decline in aortic pressure.

per kilogram and averaged 11 ± 6 ml per kilogram. Expressed in another manner, the estimated blood volumes of the individual dogs (7 per cent of body weight) increased 5 to 38 per cent, and the average increase was 17 ± 9 per cent. Systemic venous return, measured with a flowmeter in 3 dogs, rapidly decreased after the injection. Venous return then slowly increased until it again equaled systemic

arterial flow after approximately 5 minutes (Fig. 4). The volumes of blood in the animal and in the extracorporeal circuit remained stable after the initial shift, and during the 30 minute period of observation the blood originally taken up by the animal was not returned to the oxygenator, indicating that the increased capacity of the vascular compartment persisted for at least this period of time. In both dogs in

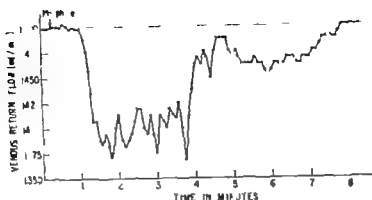


Fig. 4. Instantaneous measurements of systemic venous return recorded from an electromagnetic flowmeter in the venous return line of the extracorporeal circuit before and after the rapid intravenous administration of morphine (10 mg/kg). Systemic blood flow remained constant throughout the period of observation. An abrupt decrease in the volume of venous return occurred immediately after the drug was given and then slowly rose until it equaled systemic arterial flow after approximately 5 minutes. During the period of observation, however, the blood taken up by the animal was not returned to the oxygenator and increased capacity of the vascular compartment persisted during this time. In this experiment the volume of blood pooled indicated by the integrated area of the flow curve was 404 ml.

which it was measured portal venous pressure fell 15 to 30 seconds after the administration of morphine and remained below the control level for 30 seconds in one animal and for 2 minutes in the other. The decreases in portal venous pressure were simultaneous with those in arterial pressure and venous return and portal venous pressure was low or normal in both dogs when maximum pooling had occurred. In one animal portal venous pressure remained normal throughout the remainder of the observation period whereas in the other a transient increase with a maximal pressure 4 cm H₂O above control was observed between the fifth and tenth minutes after injection.

B. Venous tone determined by major vessel occlusion ranged from 5.3 to 9.5 and averaged 6.8 ± 1.3 cm H₂O in the 8 dogs under control conditions (Table II). After the administration of morphine venous tone fell in every animal (Fig. 5) and the average value determined 5 to 15 minutes after injection was 3.5 ± 1.1 cm H₂O ($p < 0.1$). Serial measurements during the remainder of the observation period indicated no significant change in venous tone and the decrease persisted for at least 30 minutes. The decreased vena caval pressure during major vessel occlusion observed in every animal after morphine

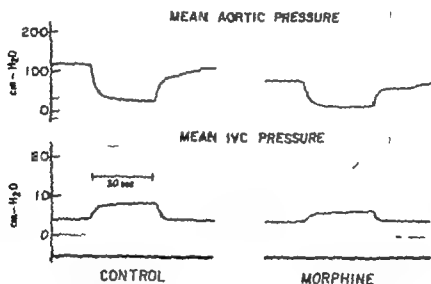
cannot be related to effects of the drug on resistance vessels since it has been demonstrated that the venous system is isolated from influences of the arterial circulation during the period of occlusion.¹⁰ The mean arterial pressure was lower after the administration of morphine in 7 of the 8 dogs but the decreases were modest and the average change was only -14 cm H₂O.

Discussion

The present studies demonstrate that in the dog the intravenous administration of morphine results in an immediate and significant decrease in total peripheral vascular resistance. Morphine also increases the capacity of the total peripheral vascular compartment and the observed decreases in venous tone indicate that the increased volume of blood is largely contained within capacitance vessels. The investigations do not however provide conclusive information as to whether the increased capacitance is effected by dilatation throughout the venous system or whether it is the net result of different actions of morphine upon the portal and systemic venous beds. Ross, Braunwald, and Waldhausen⁸ found that venous pooling occurred after the administration of digitalis glycosides but demonstrated that pooling did not result from venodilation.

Table 11 Venous tone determined by the major vessel occlusion technique of Bartelstone and mean arterial pressure before and 5 to 15 minutes after administration of morphine (0.5 mg/kg)

Animal	Mean arterial pressure (cm H ₂ O)		Venous tone (cm H ₂ O)		% Change in venous tone
	Before major pain	After morphine	Before morphine	After morphine	
1	130	115	5.5	2.0	-61
2	110	100	7.7	3.8	-51
3	115	95	6.0	2.0	-67
4	125	125	9.5	4.5	-53
5	125	103	6.7	5.2	-22
6	105	90	7.5	5.0	-33
7	135	120	6.5	5.0	-24
8	100	80	5.1	2.8	-45
Mean (± 1 S.D.)	118	103	6.6 ± 1.8	3.5 ± 1.1	-30 ± 15

Fig. 5 Records of mean aortic and inferior vena cava (IVC) pressures recorded before during and after a 30 second period of major vessel occlusion (Bartelstone). Venous tone, expressed as the difference in the IVC pressure before and at the end of the 30-second period of occlusion, decreased from a control value of 45 cm H₂O to 3.0 cm H₂O at 10 minutes after morphine had been administered intravenously.

but principally from hepatic venoconstriction and an increase in splanchnic blood volume. In the present experiments changes in volume were not measured separately in the portal and systemic venous beds. The fact that a rise in portal venous pressure did not accompany the increase in blood volume would suggest, however, that

hepatic venoconstriction played no important role in the venous pooling observed after the administration of morphine.

The different durations of the changes in vascular resistance and capacitance induced by morphine are worthy of comment. Total peripheral vascular resistance fell immediately after morphine was administered

but in all animals normal or even in increased resistance was noted within 30 minutes. Morphine also had an immediate effect on the capacitance vessels but these changes persisted throughout this same period of time. In previous studies morphine was shown to improve left ventricular performance and to increase myocardial contractile force.⁷ These positive inotropic effects gradually increased after the administration of morphine and were maximal at the end of a 30-minute period of observation. These actions of morphine on the heart were considered to be indirect ones and were attributed to sympathetic-adrenal discharge since they did not occur after adrenalectomy or beta adrenergic blockade. Accordingly, it might be postulated that the release of vasoactive substances from the adrenals and/or the sympathetic effectors was responsible for the progressive increase in peripheral vascular resistance which followed the initial decrease. Such a mechanism might have been expected to produce a corresponding gradual decrease in capacitance; however, and this did not occur. Thus no ready explanation can be offered for the fact that morphine has a transient effect on resistance and a prolonged effect on capacitance. It is of interest, however, that Ross and associates in their studies of the diptalaghycoendes found that these agents also had only transient effects on resistance vessels but prolonged actions on capacitance vessels.⁸

Most of the information concerning the peripheral vascular effects of morphine has been derived from experimental animals and the varying results of these investigations may be attributed at least in part to species differences. The dog was selected for the present studies not only for convenience but also because of the common laboratory animals the dog has physiologic responses to morphine that most closely resemble those of man.¹² The dose response relationship to morphine is quite different in dog and man; however, and in the dog significant effects upon the circulation result only from the intravenous administration of at least 0.5 mg per kilogram. In many studies doses of 1.0 to 4.0 mg per kilogram have been utilized and a dose of 7.5 to 100 mg per kilogram is described in one,⁴

as being moderately large. Thus the dose of morphine employed in the present experiments 0.5 mg per kilogram may be considered to be relatively small. When cardiopulmonary bypass was employed 1.0 mg per kilogram was given since the drug was diluted by the combined blood volumes of the extracorporeal circuit and the animal.

It would seem to be reasonable to compare the results of the experiments described above to some of the effects of morphine which have been noted in clinical investigations. Dres, Driggs and Comroe¹ for example studied the effects of morphine in both patients and normal subjects and found little change in the blood pressure when the subjects were supine. Vain developed hypotension however when they were tilted into an upright position and since this effect could be prevented by the prior application of elastic bandages to the legs it was concluded that the orthostatic hypotension was due to peripheral pooling of blood. The increases in capacitance recorded in the present experiments not only affirm the validity of this conclusion but indicate that venous pooling is a major pharmacologic effect of morphine which has not been well recognized.

Summary

The effects of morphine on total peripheral vascular resistance and the capacity of the peripheral vascular compartment were determined in normal dogs. In 13 animals in which systemic flow was maintained constant morphine (1 mg per kilogram) caused immediate decreases in resistance averaging 46 ± 20 per cent of the control values. The decrease in resistance was transient and normal or increased resistance was noted 30 minutes after the drug was administered. This effect of morphine on resistance vessels was indirect however since no immediate change in pressure occurred when morphine was injected into an isolated perfused vascular bed.

In 13 dogs studied during cardiopulmonary bypass the capacity of the total peripheral vascular compartment increased after the administration of morphine. Blood volume rose an average of 11 ± 6 ml per kilogram and systemic

return measured with a flowmeter rapidly decreased after the injection. Venous tone determined by major vessel occlusion in 8 dogs decreased from 6.8 ± 1.3 to 3.5 ± 1.1 cm H₂O after morphine (0.5 mg per kilo_{0.5}ram) was given. The measured changes in both capacitance and venous tone occurred promptly and persisted throughout a 30 minute period of observation.

The experiments indicate that increased capacitance and venous pooling are important effects of morphine on the circulation which have not been well recognized.

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Coarctation of the aorta and pregnancy

Herbert L. Wachtel Major MC USA*

Stephen W. Coarneckis Lt Colonel MC USA**
San Francisco Calif

Aortic rupture and other potentially fatal cardiovascular complications occur in a small but significant percentage of pregnant patients with coarctation of the aorta. Nine patients whose aortic coarctations were resected during pregnancy have been described.¹⁻⁹ In 8 the pregnancies were subsequently uncomplicated and terminated with delivery of normal infants. We are reporting an additional case. Since there is no way of predicting which women will develop serious cardiovascular difficulty, and available evidence does not indicate increased surgical risk during pregnancy, we think that resection of the coarctation should be accomplished during the antepartum period.

Case report

A 20-year-old woman, grade 3 para 0, was seen initially in the antenatal clinic at Letterman General Hospital on April 17, 1964. She was in her fourteenth week of pregnancy. Since her early childhood, she had been troubled with headaches and cold feet and exercise-induced aching in the triceps surae muscle groups. There was no history suggestive of cardiac decompensation. The patient was unaware of the presence of hypertension or cardiovascular disease.

On physical examination, the blood pressure in both upper extremities was 180/110 mm Hg. Femoral pulses were markedly diminished and no blood pressure was obtainable in the lower extremities. There were no signs of cardiac failure. Normal

sinus rhythm was present. There was no clinical cardiomegaly. The second sound in the pulmonary area was physiologically split. A Grade 3/6 harsh systolic murmur was heard at the base of the heart and could also be heard posteriorly medial to the left scapula. The electrocardiogram was normal. The chest x-ray film showed notching of the lower margin of the rib bilaterally. The cardiac silhouette was normal.

A diagnosis of coarctation of the aorta was made and the patient was scheduled for urgent extirpation of the coarctation, which was accomplished during the eighteenth week of pregnancy. A narrow segment of severely coarcted aorta was found immediately distal to the origin of the left subclavian artery. The coarcted segment together with small portions of aorta proximal to it were excised and an end-to-end anastomosis was accomplished. Careful microscopic examination of the specimen revealed no cystic changes in the media.

The postoperative course was uncomplicated and the patient was discharged from the hospital 2 weeks after operation on no medication. Her femoral pulses were normally palpable and she was normotensive. Normal blood pressures persisted during the rest of her pregnancy. On October 12, she went into labor spontaneously and was delivered of a normal female infant weighing 6 pounds and 6 ounces. A mid forceps rotation and delivery were performed. The postpartum course was uncomplicated and she remained normotensive.

Discussion

It is well established that untreated coarctation of the aorta frequently results in premature death. In the series of Reifenschein and colleagues,⁹ 61 per cent of 104

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Assistant Chief of Vascular Service, Letterman General Hospital, San Francisco, Calif. Present address: Cardiology Service, W. H. Hunt, Jr., General Hospital, No. 628, El Paso, Tex.

**Chief of Cardiovascular Service, Letterman General Hospital, Clinical Professor of Medicine, University of California School of Medicine, San Francisco, Calif.

patients who had survived infancy did not live beyond 40 years of age. The four common fatal complications are dissecting aneurysm and rupture of the aorta, congestive heart failure, bacterial endocarditis, and rupture of an intracranial arterial aneurysm.

Mendelson⁸ in 1960 reviewed the literature and found 200 cases of aortic coarctation associated with pregnancy. There were 14 deaths. Causes of death were aortic rupture in 8 patients, congestive heart failure in 2 patients, cerebrovascular accident in 2 patients, and bacterial endocarditis in 2 patients. Twenty-three additional cases have since appeared⁹⁻¹² with no maternal deaths. Thus 14 deaths have been reported in 223 cases, a mortality rate of 6.3 per cent.

Forty of the 200 patients described by Mendelson⁸ had cardiovascular complications during pregnancy, an incidence of 21 per cent. These complications included heart failure, aortic rupture, cerebral accident, bacterial endocarditis, toxemia, and dissecting aneurysm of the aorta. In a recent report¹³ a high incidence of nonfatal cardiovascular renal complications including cardiac decompensation, pedal edema, dyspnea, hypertension, and albuminuria were noted. These complications were present in 16 of 32 pregnancies. In contrast 19 of 21 pregnancies occurring after resection of the coarctation were free of cardiovascular renal problems.

There appears to be an increased incidence of dissection and rupture of the aorta in pregnancy regardless of the presence of coarctation. In the series of Schnitzer and Bayer¹⁴ 24 (48 per cent) of 49 women under 40 years of age who sustained aortic dissection were pregnant. In another series¹⁵ consisting of 70 females under 40 years of age who sustained aortic dissection 36 (51 per cent) were pregnant. Of 25 women with aortic dissection reported by Hirst and co-workers¹⁶ 12 (48 per cent) were pregnant. Thus a double predisposition to aortic dissection and rupture is present in pregnant women with coarctation of the aorta.

The increased incidence of aortic dissection in the two situations may have a common anatomic basis. In the series of Hamilton and Abbott¹⁷ the aortas of 13 patients with coarctation who died of dis-

section and rupture were examined histologically. In 12 cases marked changes in the media were seen with interruption and diminution of the elastica and hyaline and fatty degeneration. Hirst and colleagues¹⁶ described similar changes in each of 7 patients who died of dissection and rupture. They also reported histologic studies in 7 patients who died during pregnancy of causes other than aortic dissection. Accumulations of mucoid material in the aortic media, most prominent in the ascending aorta and the arch, were found in 6 patients. Similar abnormalities in pregnant patients with aortic coarctation who die of aortic rupture have been noted by other workers.¹⁷⁻¹⁸ The pathogenesis of these medial lesions is not well understood.

Mendelson⁸ in a review of the literature found 51 cases in which the coarctation had been resected prior to pregnancy. There was no maternal death during pregnancy in these patients. Mortensen and Ellsworth¹ described 8 patients who conceived after their coarctations had been resected. There were 21 pregnancies with no maternal mortality. On the other hand Jordan¹⁹ reported the case of a woman who sustained an aortic dissection with rupture during pregnancy 6 years after surgical correction of her aortic coarctation. The dissection occurred in the ascending aorta, the site of operative anastomosis was undisturbed. Thus one maternal death has been described in 60 patients, a mortality rate of 1.7 per cent, which is significantly lower than the 6.3 per cent mortality when pregnancy and coarctation are present without correction of the latter.

Mendelson²⁰ in 1940 suggested that therapeutic abortion and sterilization were indicated in patients with aortic coarctation who became pregnant. As more cases were reported it became obvious that the prognosis was not so grave as had been suspected. This knowledge coupled with the advent of corrective surgery resulted in a more conservative approach. In 1955 Rosenthal¹ recommended resection of the coarctation if the pregnancy was less than 20 weeks in duration. If the diagnosis was made in the latter half of pregnancy, he recommended close observation with surgical correction several weeks after delivery. In more recent years several work-

ers^{11,12} have advised no surgical therapy during pregnancy regardless of its duration at the time the coarctation was discovered. Mendelson¹³ thinks that the pendulum has swung excessively toward the conservative approach. In his opinion the relatively high morbidity and mortality rates in coarctation associated with pregnancy justify correction of the coarctation during the antepartum period.

The mortality rate in resectional surgery for aortic coarctation is low. Schuster and Gross⁴ reported a mortality rate of 4.1 per cent in 487 operations. They stated that in the absence of extremes of age and other cardiovascular abnormalities patients with coarctation could be operated upon with a risk of less than 2 per cent. At Letterman General Hospital 13 cases of post-ductal coarctation have been surgically corrected since 1960. There has been no mortality. Resection is advised on diagnosis in most cases.

Ten patients including the one reported on here in whom resection of the coarctation was accomplished during pregnancy have been described.¹⁴ Nine patients had subsequently normal pregnancies with delivery of normal infants. In Eastman's patient⁴ in whom surgery was performed during the first month of pregnancy, an aneurysm developed at the anastomotic site and ruptured during the seventh antepartum month resulting in death of mother and fetus. Whether gestational factors contributed to the appearance of the aneurysm is of course unknown.

The cases that have been described do not suggest increased surgical risk during pregnancy. There is no evidence that aortic surgery has a deleterious effect on the fetus. The mortality rate from cardiovascular complications in pregnant patients with aortic coarctation is 6.3 per cent; the morbidity rate is 21 per cent. Since it is not possible to predict which women will develop serious cardiovascular difficulty, we think that resection of the coarctation should be accomplished during pregnancy.

Summary

A case of coarctation of the aorta in a pregnant patient is reported. The coarctation was surgically corrected during the eighteenth week of pregnancy with a sub-

sequently uncomplicated pregnancy and delivery. This is the tenth patient described in whom resection of the coarctation was accomplished during pregnancy. The subject of coarctation of the aorta associated with pregnancy is reviewed. The incidence of cardiovascular complications is about 20 per cent. Since there is no way of predicting which patients will develop cardiovascular difficulty, we think that surgical correction of the coarctation should be accomplished during the antepartum period.

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Constrictive pericarditis associated with hemangioma of the pericardium

Charles Wender MD*

Joseph E Acker Jr MD

Atlanta Ga

The low incidence of primary pericardial tumors has been acknowledged. The rare involvement of the pericardium by an endothelial tumor has been reviewed by Hicken¹. He collected from the world literature 12 cases of isolated hemangiomas involving the pericardium. He included his own case of 36 year old man who had multiple hemangiomas of the visceral and parietal portions of the pericardium with associated hemopericardium and eventual death.

This paper is the second report of multiple hemangiomas involving the pericardium but the case is unique because of two features (1) multiple involvement of the pleura, thymus and pericardium and (2) pericardial constriction.

Case report

GF, a 18-year-old white girl was admitted to the University of Tennessee Memorial Research Center and Hospital on Oct 31 1963 with a productive cough that had been present for 10 months and that previously had been treated as bronchitis and pneumonia. Findings at hospitalization were: wheezes on May 5 1961 were marked cardiomegaly and pulmonary congestion. Treatment with digitalis steroids and antibiotics resulted in little improvement. Hepatosplenomegaly tachycardia and intermittent pedal edema were later noted and responded temporarily to mercurial diuretic. Progressive deterioration occurred on ep of bed rest and intensive treatment.

Examination at the time of admission revealed an extremely dyspneic pale chronically ill white girl with cyanosis. The blood pressure was 176/80 mm Hg. Pertinent findings were: encephalic tachypnea moist rales expiratory wheezes cardiomegaly without murmurs liver enlarged 10 cm below the right costal margin splenomegaly pitting pretibial edema no clubbing of the fingers and no pericardial rub or knock.

The findings were normal for all of the following: complete blood count Venereal Disease Research Laboratory test sheep red blood cell agglutination test L.E. preparations bleeding and clotting times blood urea nitrogen serum electrolytes SGOT SLDH perian urine and blood cultures histoplasma complement fixing antibodies and tuberculous biopsy cultures and coconidiomycosis. Skin tests: Histoplasma skin test was positive. The corrected Wintrobe sedimentation test was 21 mm in 1 hour and urinalysis included 10 to 12 leukocytes and 8 to 10 erythrocytes per high power field. The antistreptolysin-O titer was 333 Todd units. Prothrombin time was 18.1 seconds with a control of 13 seconds. Serum protein electrophoresis showed a total protein of 6.37 and albumin of 2.4 Gm per 100 cc. Low voltage sinus tachycardia and S-T changes due to digitalis were noted on serial electrocardiograms. Severe pulmonary congestion and cardiomegaly were seen on x-ray films. The encephalic pressure was 180 mm of saline rising to 230 mm with pressure on the right upper quadrant. The arm-to-tongue Decholin circulation time was 17 seconds.

Treatment with bed rest sodium restriction digitalis and mercurial diuretics resulted in a loss of weight from 112 to 101 pounds but dyspnea fine pulmonary rales and hepatomegaly persisted. The pressure (mm Hg) recorded by right heart

From the University of Tennessee Memorial Research Center and Hospital, Knoxville, Tenn.
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*Oldham Emory University Clinic, Department of Internal Medicine Atlanta, Ga., 30322

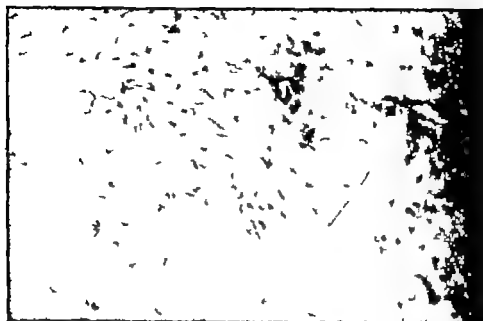


Fig. 1 A section from the pericardium shows the capillary and cavernous appearance of the hemangioma. The extra cellular fibrous reaction is evident.



Fig. 2 An additional section from the pleura shows a similar involvement.

catheterization were right atrium 34/19, right ventricle 42/20, pulmonary artery 40/22, and mean pulmonary capillary 24.

A diagnosis of constrictive pericarditis of an determined etiology was made and surgery was undertaken on Nov. 12, 1963. A median sternotomy was performed and at once a large, upper mediastinal mass thought to be thymus was noted.

Multiple small vascular lesions were seen in the pericardium, visceral pleura and parietal pleura. Frozen sections were studied and were reported to show hemangiomas of the visceral pleura and pericardium. The pericardium was markedly thickened and constricted both ventricles; however, it was removed with relative ease. Immediately after pericardiectomy the venous pressure fell from 230

to 80 mm of saline. Despite clinical improvement, tachypnea and dyspnea persisted. Digitalis and oral diuretics were continued after the patient was discharged on Dec. 14, 1962.

The final pathologic interpretation was cavernous and papillary endothelial structures with intense fibroblastic proliferation.

On Jan. 1, 1964, she was readmitted in the hospital with marked dyspnea and orthopnea. The blood pressure was 126/70 mm Hg with no pulse; pericardium noted. Other findings were: heart rate 140, respirations 27, temperature 98.4 F, systolic distention of the neck veins, lower costal bulging and flurries to percussion with absent breath sounds in both lung bases, medium rales over upper lung fields, cardiomegaly with no murmur or rub hepatomegaly 10 cm below the right costal margin but no splenomegaly. On the chest x-ray film, bilateral hazy densities due to pleural effusions were noted. The hematocrit was 29 volumes per cent. A hundred cubic centimeters of dark red fluid was obtained on thoracentesis on the right side. The hematocrit of this fluid was 17 volumes per cent. Repeated bilateral thoracenteses of sero sanguinous fluid resulted each time in temporary improvement.

The pressures (mm Hg) revealed by another right heart catheterization were: right atrium mean 6, right ventricle 35/8, pulmonary artery 35/17 and mean pulmonary capillary 30.

After repeated blood transfusion, a left thoracotomy with pleurotomy was performed on Feb. 7, 1964, after which 10 cc of nitrogen gas to 6 was injected into the pleural space to cause adhesion of the visceral pleura to the chest wall. Eighteen days later the same procedure was applied to the right pleural space. The hematocrit stabilized and the heart rate slowed before the patient was discharged from the hospital on March 4, 1964.

Discussion

The associated involvement of multiple intrathoracic structures has not been a feature of other reports of pericardial hemangiomas nor has pericardial constriction been recorded as an associated finding. Puder and Daniel in 1932 first suggested that hemorrhage into the pericardium might be followed by pericardial constriction. Laazlo⁴ reported the necessity of pericardiectomy to relieve pericardial constriction 11 months after an acute myocardial infarction with hemopericardium secondary to therapy with biliary drugs coumestrol.

Pericardiectomy was also necessary for pericardial constriction in Segal and Tabaknik's cases⁵ of penetrating stab wounds of the chest, in McKusick's case⁶ after a blunt injury and in Goodkind and associates' case⁷ after blunt nonpenetrating chest trauma.

Wilson and associates in 1962 studied

the absorption of blood from the pericardial space with the use of Cr 51 labeled red blood cells. This work had been preceded by previous studies of the absorption of blood from the pleural space.⁸

Their data confirmed a slower and less complete recovery of blood from the pericardial cavity than from the pleural space. Autopsy failed to reveal significant pericardial changes whereas some pleural edema resulted from the injection of blood into the pleural space.

Ehrenkrantz and Taber⁹ pursued the significance of intrapericardial hemorrhage and resultant constriction of the pericardium by injecting autogenous blood and the lipid fraction from this blood into two separate groups of dogs. The pericardial reaction was slight in both groups. However, one dog which received the intrapericardial lipid fraction developed extensive fibrosis. This study employed only one injection rather than repeated injections of blood or lipid fraction into the pericardium.

The preceding clinical reports and studies do not afford adequate grounds on which to base an opinion about the importance of intrapericardial hemorrhage in the pathogenesis of constrictive pericarditis. Most previously reported pericardial hemangiomas have been asymptomatic and were incidental findings at autopsy. Pericardial tamponade or gross pericardial constriction by the mass of the tumor itself has been the primary feature in asymptomatic individuals. The intense pericardial constriction in our case was not the result of the tumor mass itself. The microscopic feature of the pericardium was characterized by an extensive fibrous reaction. The etiology of this fibrous reaction is not clear. However, the nature of the tumor and clinical documentation of repeated episodes of intrapleural hemorrhage make it reasonable to assume that repeated episodes of intrapericardial hemorrhage occurred.

Summary

This represents the second case of multiple hemangiomas involving the pericardium reported in the literature.

The association of intrapericardial hemorrhage with pericardial constriction has been reviewed. Further investigative work

seems to be necessary to clarify their relationship

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Double-outlet right ventricle with pulmonary valve atresia

Report on a patient surviving to age 25

J H Rogoff MD*

Wm Anthony MD*

Cleveland Ohio

This report describes the case of a 25 year old Puerto Rican woman who was found to have both great vessels arising from the right ventricle associated with two small ventricular septal defects pulmonary infundibular stenosis and pulmonary valve atresia.

The origin of both aorta and pulmonary artery completely from the right ventricle has been uncommon but has been diagnosed more frequently in the past few years. In order to be compatible with life it must be associated with one or more ventricular septal defects. In addition half of the cases are associated with pulmonary infundibular and valvular stenosis. However to the best of our knowledge this is the first case report of a patient living to the age of 25 years with the lesion associated with pulmonary valve atresia.

The abnormality also known as double outlet right ventricle was first described by Peacock¹ in 1866. Spitzer² in 1923 considered the malformation to be a type of transposition of the great vessels and proposed a phylogenetic theory to account for its development. Maule Abbott³ in a review of 1 000 congenital cardiac de-

fects recorded 2 cases in 1936. Additional cases found at autopsy have been recorded by Austley⁴ in 1952 and by MacMahon⁵ in 1953. In 1957 the first clinical classification was provided by Witham⁶ who presented 4 cases and referred to 3 others. Two of these cases were classified as the

Eschmenger type in that no pulmonary stenosis was present and 2 others in which pulmonary stenosis was present were classified as the Fallot type. One of the latter was that of a 2.64 kilogram newborn infant who failed to breathe and was pronounced dead an hour after birth. Postmortem examination revealed pulmonary valve atresia a five leaflet common atrioventricular valve and an absent atrial septum.

Neufeld⁷ in 1961 described the cases of 13 patients in whom both great vessels arose from the right ventricle with pulmonary stenosis in 3 of them. Eighteen cases without associated pulmonary stenosis were presented by Engle⁸ in 1963. 10 of these cases were diagnosed at autopsy and 8 were diagnosed during life by angiography. Miravsky⁹ in 1963 presented a series of 22 cases of double outlet

From the Department of Medical and Surgical Sciences, Western Reserve University, Cleveland, Ohio (Dr. Rogoff) and the Department of Pediatrics, Cleveland Clinic Foundation, Cleveland, Ohio (Dr. Anthony).

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Address reprint requests to Dr. Rogoff: 1113 South Dearborn, Chicago, Ill. 60614.

*Captain USAF, Beaumont AFB, Beaumont, Texas.

right ventricle and pulmonary stenosis collected from 1946 to 1963. Of these 12 were diagnosed at autopsy or at surgery, whereas 10 were diagnosed during life by angiography.

The circulatory abnormality associated with both great vessels arising from the right ventricle depends upon the presence or absence of pulmonary stenosis. If no stenosis exists there is usually no cyanosis and the patients are according to Engle⁴ clinically very similar to those with a ventricular septal defect and pulmonary hypertension. The chief manifestations are easy fatigability and dyspnea on exertion. If pulmonary stenosis is present the patients are almost always cyanotic and have a clinical course similar to that of patients with the tetralogy of Fallot complex as observed by Astley.⁴ These patients in addition to easy fatigability and dyspnea on exertion are polycythemic.

Thus the diagnosis of common origin of the great vessels from the right ventricle cannot be made from the clinical history and physical examination alone. Rather the diagnosis is suggested by electrocardiographic findings and data from cardiac catheterization. It is confirmed by angiocardiography, preferably cineangiocardiography. Several authors emphasize the point that this lesion is not usually evident from external inspection of the heart at the time of surgery, since the lesion is intracardiac and the great vessels externally may seem to be in their normal relationship. Engle⁴ reports the cases of 2 patients who were thought preoperatively to have simple ventricular septal defect but who died shortly after these defects were repaired. Only at autopsy was it found that the aorta arose from the right ventricle. Accurate preoperative diagnosis is thus essential to the successful treatment of this lesion.

Mirowski⁶ in a report of 22 cases noted several points that distinguish these patients from those with the tetralogy of Fallot. Left ventricular hypertrophy was seen in 75 per cent of these patients whereas this condition is virtually unknown in uncomplicated tetralogy of Fallot. 63 per cent had complete right bundle branch block which is very unusual in the tetralogy of Fallot. In 60 per cent of Mirowski's

reported cases the patients had first degree heart block and in 80 per cent the P-R interval was greater than 0.88 second (normal 0.75 to 0.09 second) an extremely rare occurrence in patients with the tetralogy of Fallot. Right ventricular hypertrophy present in both lesions tends to be greater when both great vessels arise from the right ventricle.

The findings at cardiac catheterization depend upon the presence or absence of pulmonary stenosis but in either case the important finding is that the pressure in the right ventricle is equal to or almost equal to the systemic pressure. Engle states that patients with ventricular septal defect and right ventricular pressure near systemic should be suspected of having aortic transposition.

Confirmation of the diagnosis preoperatively can usually be accomplished with cineangiocardiography. On the lateral view the aorta is displaced anteriorly above the right ventricle and anterior to the ventricular septum. Both great vessel opacify at the same time depending on the degree of pulmonary stenosis and on whether the pulmonary artery is in its normal position. The other important differential finding is that both semilunar valves are in the same coronal and cross sectional body planes.

Surgical therapy for this lesion has consisted of (1) Blalock-Taussig anastomosis, (2) creation of an atrial septal defect, (3) relief of pulmonary stenosis if present and (4) intracardiac surgical correction using a Teflon conduit graft. Taussig¹⁰ makes the point that the first of these procedures may be unsatisfactory in any given case because of the danger of subsequent congestive heart failure.

There have been several reports of surgical correction of this lesion. The first performed by Lillehei and reported by Lucas¹¹ in 1961 was in a 19 year old male who had no pulmonary stenosis. A Teflon patch was sutured to the lower and lateral borders of the ventricular septal defect and then to the root of the aorta in the right ventricle thereby partitioning the right ventricle from the left forming a conduit for the blood from the left ventricle to the aorta. This patient died several days after the operation of acute massive

necrosis of the liver which was thought to have been due to inadvertent ligation of the inferior vena cava during the operation.

McGoon¹ in 1961 reported a similar operation in a 7-year-old girl again with out pulmonary stenosis. Levy¹² reported the first successful case of correction in a 7-year-old girl with associated pulmonary infundibular stenosis and aortic insufficiency. The infundibulum was resected and a conduit prosthesis was inserted from the ventricular septal defect to the root of aorta. The patient left the hospital 2 weeks after the operation. Redo¹³ in 1963 reported the case of a 10-year-old girl without pulmonary stenosis who successfully underwent the insertion of a conduit fabric prosthesis.

Case report

History. A 25-year-old single unemployed Puerto Rican woman was referred to Cleveland Metropolitan General Hospital from Rio Piedras Municipal Hospital, Puerto Rico because of cyanotic congenital heart disease.

The patient who had been a very small infant had been cyanotic from birth. From the age of 1 year she had tired on any kind of exertion. Her growth and mental development had otherwise been normal but she had left school in the third grade because she could not keep up physically with the other children.

At the age of 19 years she had had a 10 to 15 episode of syncope on arising from a chair and she had been confined to bed for 6 months. During this time she had developed painful swollen knees. She also had had a single bout of hemoptysis. Right heart catheterization had been attempted but was unsuccessful. She had required phlebotomy a total of seven times in 7 months. At the age of 22 she was discharged.

One year prior to admission to this hospital the patient had begun to experience a burning precordial pain on exertion. On the morning of the day of admission she had a bout of syncope.

The family history was of interest in that the patient's mother had died of diabetes 3 months previously. Three other sisters were living and well.

Physical examination. Examination revealed well-nourished but thin woman who had a temperature of 37.4°C, pulse 104 and regular respiratory 16. The blood pressure was 130 at rest and 90 during H_2 breathing. Body weight was 44.8 kilograms and height was 147.5 cm. The lips mucous membranes and fingernails were cyanotic. There were accentuated palpitations and a prominent diffuse cardiac apex thrill. There was increased activity over the right ventricular outflow tract but a thrill was palpable. The heart was not clinically enlarged. On auscultation there were two distinct systolic clicks and Grade 3/6 harsh holosystolic

murmur beginning in mid systole and ending with a sharp accentuated single second sound heard in the second and third left intercostal spaces. A few fine dry crackling end inspiratory rales were heard over the base of the left lung. The patient had no peripheral edema but showed marked hypertrophic pulmonary osteoarthropathy. All of the joints of the extremities were hyperextensible. The knees were swollen and tender to deep palpation. The neurological examination was negative.

Because of an infiltrate in the left upper lung lobe seen on the chest film (Fig. 1) she was admitted to the tuberculosis ward.

Laboratory examination. Urinalysis revealed a specific gravity of 1.015, a trace of protein and no sugar or acetone. The urinary sediment was negative. The hematocrit was 59 per cent, the hemoglobin 16.8 Gm per 100 ml, the white cell count was 9,164 with 54 per cent neutrophils, 33 per cent lymphocytes, 12 per cent monocytes and 1 per cent basophils. Blood hematocrit and liver function tests were within normal limits. A second strength tuberculin skin test showed 14 mm of erythema and induration in 48 hours and the histoplasma skin test showed 40 mm of erythema and induration in 48 hours. Repeated throat cultures were negative. Three gastric parasites were negative for acid fast bacilli. A stool examination for ova and parasites revealed only a few Trichuris ova. An electrocardiogram revealed only right ventricular hypertrophy and atrium and sinus tachycardia (Fig. 2).

Catheterization. The data obtained at right heart catheterization and in the pulmonary function laboratory are recorded in Tables I and II. The indicator-dilution curve with injection into the right atrium and withdrawal from the right brachial artery was compatible with a large right-to-left shunt. A subsequent unsuccessful attempt at car-



Fig. 1. Roentgenogram of the chest taken at the time of admission showing the infiltrate in the left upper lobe (arrow).

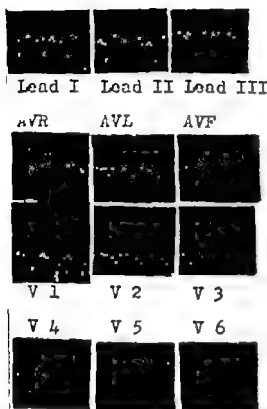


Fig. 2. Electrocardiogram taken at the time of admission shows right ventricular hypertrophy and strain with tachycardia.



Fig. 3. Roentgenogram of the chest taken during attempted right heart catheterization reveals the lesion in the left upper lung lobe in extensive bronchial circulation (confirmed at autopsy). Catheter in azygos vein film taken 6 seconds after injection of 40 cc. of contrast material.

dine catheterization revealed that the catheter was in the azygos system and that the lesion in the left upper lung lobe opacified with the azygos vein on angiocardiology suggesting an extensive bronchial circulation (Fig. 3).

Fluoroscopy. Fluoroscopy revealed that the vascular markings in the lungs were decreased bilaterally. The heart was slightly enlarged with the right ventricle being the only chamber showing enlargement. The pulmonary artery segment and aortic arch both appeared to be diminished in size. A barium swallow was negative. Cineangiography was thought to reveal extremely poor opacification of the pulmonary artery with the major portion of the contrast material passing out through the aorta. A markedly narrowed outflow tract of the right ventricle was also thought to be demonstrated. In retrospect it was seen that the aorta was anterior to the ventricular septum on the lateral view.

Operation. On the ninety-fourth hospital day the patient underwent a Blalock-Tausig anastomosis of the right subclavian artery to the right main branch of the pulmonary artery using an interposed free vein graft obtained from the right saphenous vein.

The right main branch of the pulmonary artery was approximately 3 mm. in diameter.

The patient did well for the first 36 hours after operation. She was alert and appeared to be less cyanotic. The peripheral arterial oxygen saturation rose from 60 per cent preoperatively to 72 per cent the day after the operation. However on the third postoperative day the patient had two apneic spells lost consciousness and gradually became unresponsive. Despite vigorous supportive measures she died on the fifth postoperative day.

Autopsy. Autopsy revealed that the Blalock-Tausig anastomosis was patent. Gross inspection of the heart revealed that the aorta arose from the heart more anteriorly than usual. The pulmonary artery and its branches and the aorta and its branches were normal except that the bronchial arteries were greatly enlarged.

Dissection of the heart (Fig. 4) showed that the cause of the right atrium and the tricuspid valve were normal. The right ventricular wall was greatly hypertrophied. The pulmonary artery arose in its usual position although there was marked stenosis of the pulmonary outflow tract by a large muscle mass. The pulmonary artery was cone-shaped, fibrous and atretic. The aorta arose from the right ventricle to the right of and slightly anterior to the pulmonary artery. The coronary artery ostia and the aortic valve were normal. There were two ventricular septal defects, each about 1 cm. in diameter. The upper one was below and to the right of the aortic valve, separated from it by the crista supra-ventricularis which was divided by the defect into two branches, one cephalad and one caudad to the defect. The lower septal defect was low in the muscular portion of the septum, approximately 3 cm. below the aortic valve. The left atrium and mitral valve were normal. The left ventricular wall was markedly hypertrophic. The only left ventricular outlets were the ventricular septal

Table 1 Cardiac catheterization

Pressures (mm Hg)		Oxygenation		
		Oxygen	Values per cent	Sa-O ₂ at room (°°)
Right atrium	8 mm Maximum	Arterial capacity	27.10	
	2 mm Minimum	Superior vena cava	11.14	50.5
Right ventricle	128 mm Systolic	High right atrium	11.58	52.3
	6 mm End-diastolic	Low right atrium	11.94	54.1
Brachial artery	134 mm Systolic	Low right ventricle	17.18	77.6
	92 mm Diastolic	Mid right ventricle	11.67	52.6
	105 mm Mean	Brachial artery	13.98	63.2

Table II Pulmonary function

	Performance	Comparisons
One-second vital capacity	7.37 liters	75 per cent total vital capacity
Two-second vital capacity	3.10 liters	98.7 per cent total vital capacity
Total vital capacity	3.14 liters	120 per cent Normal
Total expiration time	3.5 seconds	
Maximum breathing capacity	70 liters/min	Predicted 117 liters/min
Walking ventilation rate	15.7 L./M ² /min	Normal 7-11 L./M ² /min
D ₇ post index (walking ventilation/VBC)	0.23	Predicted 0.06-0.10

A reading to predicted value based on body surface calculated from weight and height on the Datascope records.



Fig. 7 Heart at postmortem shows hypertrophied right ventricle with aortic valve and two extracardiac septal defects (arrows).

defects. The atrial septum was intact and the ductus arteriosus was closed.

Discussion

This 25-year-old woman was thought preoperatively to have a tetralogy of Fallot complex. Her preoperative work up strongly suggested the tetralogy whereas many of the criteria for making the diagnosis of double outlet right ventricle as discussed above were unfulfilled. Nevertheless the right ventricular pressure was approximately equal to systemic pressure and a review of the cineangiocardiography after autopsy disclosed that the aorta did indeed arise anterior to the ventricular septum. Although systemic pulmonary artery anastomosis seemed to help this patient clinically for a short time it did not prevent the recurrence of anoxic episodes. The fact that there were two small ventricular septal defects one of which was located some distance from the aortic root would most likely have precluded the insertion of a conduit type of graft. Possibly the lower septal defect could have been closed and a conduit inserted between the upper defect and the aortic root. This would have had to be accomplished by widening of the pulmonary outflow tract and a pulmonary valvulotomy. Whether this would have allowed sufficient outflow for the left ventricle is a moot question because of the small size of the septal defect.

Summary

The case of a 25-year-old woman who had both great vessels arising from the right ventricle, two ventricular septal defects, pulmonary infundibular stenosis and pulmonary valve stenosis has been presented with a brief review of pertinent literature. Unusual features of this case included right ventricular hypertrophy pattern in the electrocardiogram and bronchial collateral circulation to the left lung that was thought radiographically to be tuberculosis.

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politan General Hospital. We are also grateful to Dr. F. Simeone who read and corrected the manuscript. The achievements of this paper are largely theirs; the fruits are ours.

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Clinical pathologic conference

Madison S Spack M.D.*
Arthur W Martin M.D.
James B Sudbury Jr M.D.
Donald B Hackel M.D.
Ramon I Canent Jr M.D.
Durham N.C.

Clinical abstract

This white male infant was first seen at Duke Hospital when he was 4½ months old. During the first 3 months of life he had been constipated and it was noted that his muscles were quite firm and hard. Increased sweating was noted during the third month of life and for 2 weeks prior to admission he had had episodes of crying during his feedings. His cry became weaker and prominent neck veins were observed by the parents. At birth the umbilical cord and placenta of the patient had been sent to Dr. Sudbury for analysis and alpha glucosidase was found to be absent. The past history revealed that he was the product of an uncomplicated pregnancy. A brother who died at the age of 8 months was known to have had Type II glycogenosis.

Physical examination revealed that the patient maintained a frog like position (Fig. 1). He appeared to be mildly cyanotic and was in moderate respiratory distress. He weighed 5.5 kilograms, the pulse rate was 140 beats per minute and regular. Respiration was rapid with intercostal and subcostal retractions. The left side of the chest was more prominent than the right with dullness to percussion over the entire left chest. Rales were present over the left chest posteriorly. The femoral arterial pulses were normal, the neck veins were distended and by palpation the heart seemed to fill the whole left chest. There was a Grade 2.3 apical harsh systolic murmur with a prominent third sound. The liver was palpable 6 cm below the right costal margin. The tongue was prominent. The muscles did not feel prominent or firm. No deep tendon reflexes were obtainable and there seemed to be generalized hypotonia.

The electrocardiogram (Fig. 2) revealed a P-R interval of 0.08 second with left ventricular hypertrophy evidenced by abnormally deep Q and a

tall R wave in Lead V₆. Additionally, the Q wave was abnormally deep in Lead I. The T vector was abnormally positioned to the left at approximately -15 degrees.

Laboratory studies of the blood gases normal results. Urinalysis showed 7+ proteinuria and no glycosuria.

The patient was acutely ill on admission. Despite oxygen and moisture therapy there was persistence of the cyanosis. The heart murmur became louder, labored respiration continued and the neck veins became more distended. Penicillin and streptomycin therapy was started. His condition worsened and 12 hours after admission he suddenly sat up, gagged and ceased breathing. Attempts at resuscitation were unsuccessful.

Discussion

DR. SPACK: This case concerns an infant with a classic history of Type II glycogen storage disease (Pompe disease).¹ The clinical history of gastrointestinal tract difficulty (vomiting early followed by constipation), weak muscles, enlarged tongue and typical frog like position exhibited by the patient on admission are all classic manifestations of Type II glycogenosis with accumulation of glycogen in excessive amounts in all tissues especially in the heart. This condition comes under the category of several primary cardiomyocardial diseases as discussed by Lambert and Madigan² with the development of heart failure during the first year of life, massive cardiomegaly, absence of central shunts and

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Address Department of Pediatrics, Duke University Medical Center, Durham, N.C. 27706.



Fig. 1 Typical frog like position exhibited by patient. This position is typical of infants with Type II glycogenosis.

absence of significant cardiac murmurs. This group of diseases includes anomalous origin of the left coronary artery from the pulmonary artery, endocardial fibroelastosis, myocarditis, cardiac enlargement of unknown cause, and Type II glycogenosis. Clinicians are encountering with increasing frequency many of the above mentioned conditions with presumed superimposed (secondary) endocardial fibroelastosis with the common denominator being that of an enlarged left ventricle. The apical systolic murmur in this patient becomes quite significant in this regard. Did this patient have mitral insufficiency with possible superimposed endocardial fibroelastosis or could the murmur have been related to obstruction of the left ventricular outflow tract due to massive septal hypertrophy? Ehlers and co-workers⁴ have documented in this disease the occurrence of left ventricular outflow obstruction secondary to the massive hypertrophy of

the left ventricle with bulging of the septum into the outflow tract. In this situation the clinician is presented with quite a dilemma in the face of the congestive heart failure since treatment with digitalis may increase the strength of left ventricular contraction with subsequent greater tightening of the muscular aortic ring as suggested by Hohn and associates.⁵ Thus in this disease when outflow obstruction occurs the use of digitalis may be more harmful than helpful although actual documentation of such an effect of digitalis in Pompe's disease remains to be confirmed.

The electrocardiogram is of considerable aid in distinguishing this disease from other types of primary endomyocardial pathies. Anomalous left coronary artery leads to myocardial infarction and in symptomatic patients there are the typical findings of an anterolateral myocardial infarct. Myocarditis and endocardial fibroelastosis do not exhibit the prominent Q waves in Leads I and V_4 as characteristically present

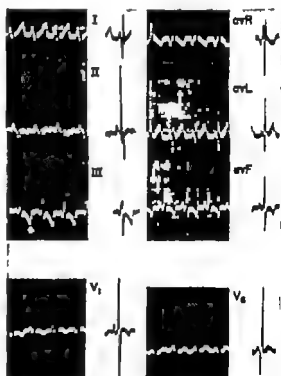


Fig. 2 Electrocardiogram of patient on film. Note the deep Q waves in Leads I, II, III, the short R interval (0.03 second) and the abnormal T waves.

in Pompe's disease (Fig 2)* Also this patient demonstrated the characteristic shortening of the P-R interval so commonly present in this condition.

Currently the classic clinical features and familial aspects of this condition are so well known that an accurate diagnosis has become much less of a problem than it was a decade ago. Possibly Dr Sedbury will comment on the value of determinations of alpha glucosidase in the cord and placenta of the newborn as an aid to earlier diagnosis. To date therapeutic measures have merely been supportive and have not significantly altered the course of the disease. Treatment of associated respiratory infections, especially pneumonia secondary to obstruction of the left bronchus as probably occurred in this patient may help slightly. In 3 patients whom we have seen with Dr Sedbury the terminal days of life were characterized by severe pulmonary infection with augmentation of congestive heart failure.

Thus although we can diagnose this condition with little difficulty at the present time we are at a complete impasse to know what to do about improving cardiac function to allow survival even past a year. That this is a progressive disease there can be little question. X-ray films and electrocardiograms in the newborn period are usually normal and most patients become symptomatic by 6 months of age. Possibly our pathologists and metabolic investigators can suggest hopeful avenues for research to improve therapy.

Dr MARTIN: Although various questions have been raised by the clinician one fact is quite certain. This child did have glycogen storage disease. Type II. Various names have been used to identify this disease. The one which best fits this condition is generalized glycogenosis. It is not a disease limited to the myocardium. In fact some of the most striking pathologic changes are found elsewhere. From a functional point of view the cardiac changes are more prominent.

The heart in this case was markedly enlarged weighing 150 grams (normal for this age is 27 to 29 grams). All chambers were dilated and hypertrophied. The right ventricular wall was 4 mm. thick and the left ventricular wall measured 1.2 cm. The

foramen ovale was anatomically patent but I do not think that this contributed to the cardiac impairment. The endocardial surface of the left ventricle was opaque and thickened (endocardial fibroelastosis) especially that overlying the base of the inter-ventricular septum. When endocardial fibrosis is present in glycogen storage disease it is more prominent in hearts of older infants than in the newborn. There was no evidence of obstruction of the left ventricular outflow tract. The mitral valve was mildly involved by the endocardial fibroelastotic changes and it is possible that mitral insufficiency may have accounted for the prominent apical murmur noted by the clinicians.

Cardiac enlargement such as this must be considered to be a space occupying lesion. Grossly the heart was seen to occupy almost the entire left chest. The left lung was compressed posteriorly and was almost totally atelectatic—only the very tips of the apex and base were crepitant. The left main stem bronchus was flattened by the enlarged heart having only a slit like orifice. Microscopically this lung showed marked atelectasis.

The right lung was quite different. Grossly it appeared to be normally crepitant but microscopically there were widespread areas of bronchopneumonia, chronic congestion and pulmonary edema. In addition the right bronchus and segmental bronchi as well as the trachea and pharynx were filled with vomitus. The stomach was markedly distended with similar material. The material did not enter the left bronchus because of its compression by the heart. This aspiration of vomitus probably occurred as an agonal event. It must be emphasized that in addition to the obvious cardiac problems in this case this patient had marked respiratory impairment.

Microscopically the myocardium showed the typical lacework pattern in longitudinal section and a honeycombed appearance in cross section (Fig 3). There was marked vacuolar formation in the central portions of the myofiber especially about the nuclei. The nuclei however appeared to be essentially normal. Stains for glycogen showed diffuse deposits within the vacuoles as well as the fibrillar portions of these cells. These changes in the myofibers

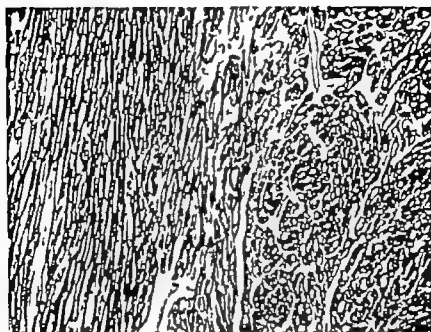


Fig. 3. Electron micrograph of myocardium showing generalized glycogenosis. There is the prominent honey combed pattern in longitudinal section and honey combed pattern in cross sections. Hematein and eosin $\times 120$.

were present throughout the myocardium.

The liver also was enlarged, light yellow and soft and weighed 265 grams. Microscopically the liver contained much stainable glycogen but otherwise appeared to be within normal limits. Recent work by Brudhuim Herra and Loeb⁷ has shown that much of this hepatic glycogen is found within membrane lined vacuoles which they refer to as lysosomes. Structurally this glycogen appears to be the same as that found elsewhere in the cytoplasm. The vacuole bound glycogen as well as the free cytoplasmic glycogen is digested by amylose in vitro. It appears therefore that the lysosomes have accumulated glycogen and have been unable to subsequently utilize this glycogen. It is proposed that this is due to the absence of an alpha glucosidase in these lysosomes which normally would have readily hydrolyzed the glycogen.

Similar electron microscopic studies were carried out on the heart and skeletal muscle from the patient. With certain reservations concerning fixation with formalin and possible postmortem changes a few reasonable comments can be made concerning these tissues. In Fig. 4 a representative

section of heart is illustrated. This is a longitudinal section and about the nucleus there are several vacuoles of granular material resembling glycogen as it would appear in more properly fixed specimens. These masses of material are incompletely surrounded by a membrane. Allowing for artifacts in preservation caused by formalin fixation one can assume that these masses may have been completely surrounded by a membrane similar to that shown for the liver. Certainly it can be said that in the heart of this patient there was the accumulation of masses of cytoplasmic material presumably glycogen and that here too this material may have been within lysosomes.

Aside from the pathologic changes described thus far the most striking changes at least histologically were seen in skeletal muscles (Fig. 5). As is true in most cases of generalized glycogenosis the skeletal muscles of this child were grossly unremarkable. However microscopically there was widespread vacuolar dilatation and degeneration of long segments of myofibers with clumps of basophilic material at the periphery of the fiber frequently well



Fig. 4 Electron microcopy of heart in generalized glycogenosis. There are several acinar masses near the nucleus composed of finely granular material and partially surrounded by membrane. There is preservation of the normal myofibrillar pattern. Phosphotungstic acid $\times 10,000$.

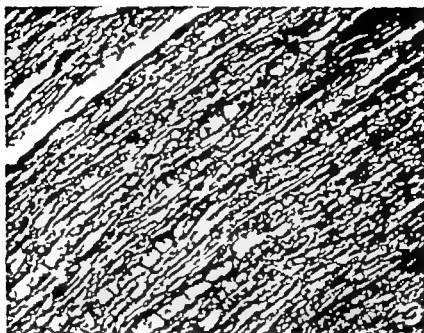


Fig. 5 Skeletal muscle in generalized glycogenosis. There is a widespread vacuolar degeneration with accumulations of acid mucopolysaccharides in the myofibers. Hematoxylin and eosin $\times 120$.

of this material extended across the damaged fibers and the nuclei in these areas appeared to be pyknotic. Much glycogen could be demonstrated in these damaged cells by histochemical methods as well as in the adjacent more normal fibers. Other staining techniques showed that these damaged fibers contained an acid mucopolysaccharide present in the basophilic material as seen with hematoxylin and eosin. Fig. 6 shows the electron microscopic features of skeletal muscle fibers in this patient. In the upper right hand corner is a portion of an adjacent normal fiber which

shows good preservation of the myofibrillar structure. In the damaged fiber there are masses of granular material surrounded by fragments of a membrane as was demonstrated in the heart. In addition there is a conglomeration of material composed of portions of granular material adjacent to the sarcolemmal membrane. Occasionally this material extends in strands or masses across the fiber. The location of this material coincides with the position of the acid mucopolysaccharides as seen by light microscopy. These changes are not unlike that seen in early necrosis of muscle. One thing is clear from these electron micro-

scopic studies that is it appears that pathologically the skeletal muscle is more severely damaged than is the heart whereas clinically the cardiac changes are far more striking.

In closing I would like to emphasize again that this disease is not merely glycogen storage disease of the heart but rather is a manifestation of widespread impairment in glycogen metabolism affecting many organs and tissues. Whether widespread accumulation of glycogen in other organs leads to functional impairment is difficult to determine. But it would seem to be more appropriate to refer to this disease as generalized glycogenosis rather than glycogen storage disease of the heart.

DR SIDBURY: The pertinent biochemical findings on the postmortem tissues (Table I) are the markedly elevated concentrations of glycogen in the tissues and the absence of acid (lysosomal) alpha glucosidase. The glycogen is normal as characterized by beta amylase. The phosphorylase values are lower than those values found in biopsied tissue as expected. It is of interest that the kidney has the least glycogen of those organs which might be expected to



Fig. 6 Electron microscopy of skeletal muscle in general and glycogenosis. There are several sarcolemmas containing finely granular material and partially surrounded by a membrane. There is also a conglomerate of granular material and mitochondria and absence of normal myofibrillar pattern. A portion of a more normal myofibril is in upper right hand corner. Phosphotungstic acid $\times 10,000$.

Most of the diseases resulting from a detectable enzymatic defect in children have a genetic basis and generally the mode of transmission is recessive. Table II is a tabulation of the familial occurrence from our experience and that reported in the literature (stillborn infants excluded). Obviously parents and grandparents could not be affected since the disease is lethal in the early years of life hence only siblings would be at risk. It will be seen that the incidence in families with an affected child is approximately 50 per cent which is twice the predicted 25 per cent of the Mendelian ratio for recessives. By the method of deletion of the proband the expected 25 per cent expected in these families is very nearly achieved here. Note worthy also is the distinctly increased incidence of consanguineous marriages in these families when compared with the general population further supporting the postulation of a recessive condition.

An attempt has been made to estimate the gene frequency in North Carolina which has a relatively stable population. Information was solicited in regard to such patients from pediatricians and pathologists throughout the State and the records of the State Vital Statistics Division were canvassed. There were 1,560,679 live births between 1950 and 1963 and 4 patients with the disease were detected during this period. This would give a frequency of the disease of about 1 in 400,000 live births or 1 heterozygote in 300 persons.

Theoretically the most hopeful approach to therapy would be the administration of an agent which would make the lysosomes leaky and either permit the glycogen to leak out or glycogenolytic enzymes to gain ingress. Such an agent might be administered from time to time. One of the less toxic detergents may qualify but careful animal toxicity data would be needed before such an approach was attempted.

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Fundamentals of clinical cardiology

Enzymatic profile of myocardial infarct

John G. Butsakis M.D.*

Russell O. Briere M.D.**

Ann Arbor, Mich.

And thick and fast they came at last
And more and more and more

Wine Through the Looking Glass
Lewis Carroll

The causal relationship between the rise in activity of certain enzymes in the serum and the occurrence of damage to the myocardium has been established without question. Experiments and histochemical investigations have shown that in infarcted heart muscle is rapidly depleted of various enzymes and that these enzymes appear in an active form in the blood that drains from the infarcted myocardium.

Rapid clinical utilization of these observations followed the report by LaDue and associates¹ in 1954 that serum glutamic oxalacetic transaminase (SGOT) is elevated after an acute myocardial infarct. As indicated in the preamble to this report many other enzymes have been tested for their applicability in the confirmation of the diagnosis of myocardial infarct. The myocardium is a rich source of enzymes and in addition to SGOT elevations of the malate and lactate dehydrogenases, aldolase, phosphoglucose isomerase and creatine phosphokinase are usually present after infarction of cardiac muscle.

To the present time however only five enzymatic assays have withstood critical clinical and laboratory investigation. These

are the measurement of (1) serum glutamic oxalacetic transaminase (SGOT), (2) serum lactic dehydrogenase (SLD), (3) isoenzymes of serum lactic dehydrogenase, (4) serum α -hydroxybutyric dehydrogenase (SHBD) and (5) serum creatine phosphokinase (CK-MB).

Transaminases Human tissues and serum contain two transaminases of clinical importance: SGOT and glutamate pyruvate transaminase (GPT). They catalyze the reversible transfer of an amino (NH_2) group from an amino acid to a receptor keto acid yielding a new amino acid and a new keto acid.

Aspartate + Lactoglutarate $\xrightleftharpoons{\text{GOT}}$ Glutamate + oxalacetate

Alanine + Lactoglutarate $\xrightleftharpoons{\text{GPT}}$ Glutamate + pyruvate

The heart and liver are especially plentiful in GOT but the liver contains much more GPT than does the heart. Thus the SGOT may be expected to be increased when either of these organs is damaged, but an elevation of SGPT is typical of hepatocellular damage only.

Lactic dehydrogenase This enzyme is widely distributed throughout most body tissues and catalyzes the reaction:

Lactate + nicotinamide — adenine dinucleotide (NAD) $\xrightleftharpoons{\text{LDH}}$ pyruvate + reduced nicotinamide — adenine dinucleotide (NADH₂)

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Received for publication Dec. 13, 1963.
Associate Professor of Pathology.
** Associate Professor of Pathology.

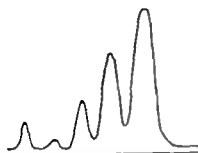


Fig 1 Densitometric tracing of a lactic dehydrogenase electropherogram obtained from a patient manifesting an acute myocardial infarct. Note (1) the elevated fast (anodic) isoenzymes and (2) the clear discrimination between these myocardial fractions and the cathodic hepatic isoenzymes.

Lactic dehydrogenase isoenzymes Lactic dehydrogenase in concert with other enzymes is not a uniform enzyme but rather occurs in a number of molecular species. These differ in their primary structure i.e. amino acid sequence yet possess the same action and substrate specificity (L lactate). The enzymatically active fractions (isoenzymes or isozymes) can be separated by a variety of means. Under the conditions of electrophoresis (starch gel agar gel or cellulose acetate) normal human serum is separable into five distinct isoenzymes.² Tissues with a high aerobic metabolism such as cardiac muscle have a high content of fast migrating (anodic) isoenzymes. Conversely slow migrating (cathodic) fractions predominate in the liver.³ The heart and liver fractions occupy extreme poles of the diagram and may be readily distinguished (Fig 1).

The five isoenzymes are produced by a random tetrameric association of two different polypeptide subunits which are considered to be under separate genetic control.⁴ The first and fifth are homogeneous tetramers whereas the three intermediate bands are heterogeneous or hybrid forms. This suggests that in fact only two principal or parent forms of LDH exist. All possible combinations of these two monomers are produced (Table I).

The clinical laboratory and diagnostic importance of this molecular heterogeneity lies in the fact that a differential evaluation of an elevated total SLD may be possible

Table I Tetrameric molecular association of the two principal polypeptide subunits of lactic dehydrogenase

Monomers				
AA AA	AB AA	AB AB	BB AB	BB BB
LDH	LDH ₁	LDH	LDH	LDH ₁

when there is concomitant injury to several tissues.

Alpha hydroxybutyric dehydrogenase (HBD) It has been shown that lactic dehydrogenase does not possess an absolute specificity for its usual substrate but can also convert the oxo group of ketobutyric acid in the alpha position to the hydroxy group.⁵ The fast migrating SLD isoenzymes exhibit much greater ability than do the slow fractions to reduce α ketobutyrate relative to their activities with pyruvate as substrate. In deference to the reaction with α ketobutyrate the catalyst has been designated α hydroxybutyric dehydrogenase (HBD).⁶ At present it is not known what kind of enzyme one is measuring when the assay for SHBD activity is performed but the measurement has been equated with a chemical differentiation of the fast migrating SLD isoenzymes.⁴

Creatine phosphokinase (CPK) CPK catalyzes the reversible transfer of a high energy phosphate group from adenosine triphosphate (ATP) to creatine



The enzyme is found principally in skeletal and heart muscle and also in lesser amounts in brain tissue, kidney, liver, lung, pancreas and the erythrocytes have virtually undetectable amounts of CPK activity.⁷ The distribution in human tissue has led to the consideration of serum CPK activity as the most specific and sensitive serum enzyme test currently available for the confirmation of disease or injury to

skeletal muscle and myocardium.⁷ In diseases of skeletal muscle with particular reference to the dystrophies the estimation of CPH is the measurement of choice and studies in patients with muscular disorders underscore the value of estimation of CPH in the differential diagnosis between progressive muscular dystrophy and atrophies of neurogenic origin.⁸

Clinical application

Any evaluation of the clinical applicability of an enzyme assay must perforce be a consideration in three fundamental and interrelated areas of consideration: (1) ease of assimilation into the diagnostic laboratory, (2) specificity and sensitivity of the enzyme being measured, and (3) duration of the enzyme's activity in sera after tissue injury.

Laboratory performance. The estimation of the activity of SCOT, SLD, and SHBD may be determined satisfactorily by either spectrophotometric or colorimetric assays. The former has inherent chemistry

advantages but equal clinical information is derived from both types of assay. As of the present colorimetric assays of CPH cannot be recommended and are distinctly inferior to ultraviolet spectrophotometric methods.⁹

The electrophoretic separation of SLD isoenzymes is diagnostically superior to techniques relying on heat stability of the fractions. Cellulose acetate fractionation is within the technical ability of any routine laboratory and is readily suited for either a quantitative or qualitative evaluation after separation of the isoenzymes.¹

Enzyme specificity. There is no enzyme activity measurable in serum which is specific for heart muscle alone. Specificity then becomes a subject of relative evaluation. In decreasing order of relative specificity the enzymes may be listed as follows: CPH, isoenzyme of LDH, SHBD, SCOT, and SLD.

The nonspecificity of SLD is well known. Table II, listing the tissue activity levels of CPH and (COT) may be considered to represent the two extremes of the relative specificity scale. Table III emphasizes the absence of CPH activity within the erythrocyte, a very important feature when one is considering the effect of hemolysis on serum activity levels.

Early reports attested to a high degree of specificity for heart muscle manifested by α -hydroxybutyric dehydrogenase.^{10,11} As clinical and diagnostic experience with the assay was gained, this enhanced specificity was found to be only relative. It is superior to the measurements of SCOT and SLD.¹ Fig. 2 indicates that elevations above normal may occur in a variety of disorders other than myocardial infarct. Elliott and Wilkinson¹ have reported to the use of an SHBD/SLD ratio in the differentiation of myocardial disease from other disorders in which the SHBD is elevated. Investigation in our laboratory¹² and that of Rosalki¹³ have not substantiated this discriminatory capacity of the ratio.

Fractionation of the isoenzymes of lactic dehydrogenase has markedly increased the sensitivity and specificity of that enzyme in clinical diagnosis. The various fractions have been designated numerically according to their primary sources as follows:¹⁴

Table II

COT activities of human tissues ¹⁵		CPH activities of human tissues ¹⁶	
Heart	7,800	Skeletal muscle	18,400
Liver	7,100	Heart	5,550
Skeletal muscle	5,000	Brain	3,400
Kidney	4,500	Adrenal gland	136
Lung	1,400	Lung	0.5
Spleen	00	Liver	0
Lung	500	Prostate	0
Red blood cell	15	Erythrocyte	0
Serum	1	Serum	0

Relative activity of liver to heart in (COT) and myocardial to skeletal muscle (CPH) (each $\times 10^{-3}$ mg)

Table III Normal erythrocyte and serum content of enzyme activity

	COT	LDH	SHBD	CLA
RBC/serum content	8/1	1,000/1	1,000/1	0

SHBD ACTIVITY LEVELS IN CLINICAL DISORDERS

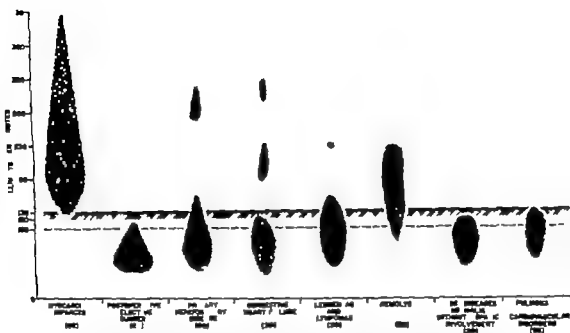


Fig. 2. Although SHBD activity may be considered to be more specific for myocardial lesions than the SGOT or SLD, false positive levels are seen in hepatobiliary disorders, congestive heart failure and hematopoietic disorders, especially hemolysis. Note, however, the absence of false negatives in the 66 cases of documented myocardial infarct. In the University of Michigan series, all infarcts have produced activity levels above 120 mU/liter.

1 from skeletal muscle and liver, 2 and 3 from lungs, 3 and 5 from the pancreas, 3 and 4 from the lungs, 3, 4 and 5 from the kidney, 4 and 5 from cardiac muscle.

In actual laboratory and clinical practice, similar and often identical patterns for myocardial infarct are seen in patients manifesting infarcts of the kidney, patients with pernicious anemia or lymphomas with hemolytic anemia, and patients suffering from progressive muscular dystrophy.² To emphasize the effect of hemolysis, a common practice is to use hemolyzed serum as a positive control for electrophoretic separations.

Enzyme sensitivity. Under the proper conditions of appropriate selection of test and due consideration of the duration of activity in sera, all five procedures will yield positive results. False negatives are rare and may be attributed to laboratory error in most instances.¹¹ SLD isoenzyme fractionation appears to have a superior sensitivity. The appearance of a positive increase in the first fractions may indicate

both electrocardiographic changes and a rise in the total enzyme activity in the serum. Ten from our series of over 2,000 programs have manifested this phenomenon, and the experience of Freeman and Opher¹² corroborates these observations.

Refrance on the estimation of the total activity in sera alone may be misleading in the discrimination between superimposed congestive heart failure and a second infarct or extension of the primary myocardial infarct. In these instances, isoenzyme fractionation and/or estimation of CPH offer considerable assistance in the former by the emergence of a hepatic band in the program and in the latter by an additional peaking after normalization has occurred. The absence of CPH in the liver makes a secondary rise in activity almost pathognomonic of a superimposed or extended myocardial infarct.

Enzyme release and duration of activity. After an initial elevation following myocardial infarction, enzyme activity in serum declines rather rapidly, and

Table IV Reaction time or release activity span in serum after uncomplicated myocardial infarction

Enzyme activity in serum	SGOT	SLD	SHBD	SCPA
Onset of rise	12 hr	12-24 hr	12-24 hr	3-4 hr
Return to normal	4 day	7 days	10 days	3 day
Peak X normal	4-2	3-6	4-8	11
Time of peak	24 hr	12 hr	72 hr	33 hr

lives of the enzymes important in the diagnosis of myocardial infarct are short, i.e. the enzymes are rapidly eliminated or inactivated. It may be seen then that although a normal serum activity level in the course of serial determinations excludes the presence of a fresh or superimposed infarct, it does not, depending upon the time of collection, exclude the diagnosis of an initial myocardial infarct.

Table IV summarizes the average time reaction span and peaks of the serum activity of four of the five enzyme assays under consideration. After a myocardial

infarction activity increases in the serum in the following order: (1) CPK, (2) GOT, (3) LD, and (4) HBD. The return to normal levels also follows this sequence. Serum CPK begins to rise before any of the others, often as early as 3 to 4 hours after the infarction. Peak activity is usually reached at 36 hours, followed by a rather precipitous drop to normal levels by the second to the fourth day. The length of time during which SGOT is elevated after the infarction is relatively short—average of 4 to 5 days—and although SLD is elevated for a longer time, SHBD remains at abnormal levels the longest—10 to 15 days. Large myocardial infarcts may cause persistence of abnormal levels of SHBD for as long as 5 to 10 days after the total enzyme activity of SLD has normalized¹¹ (Fig. 3). If restricted to the choice of one specimen, it would appear to be wisest to delay sampling until the period 24 to 36 hours after infarction. It is this time period which will give the greatest likelihood of obtaining abnormal values for all enzyme activity.

Conclusions

There is no enzyme activity measurable in serum which is specific for myocardial

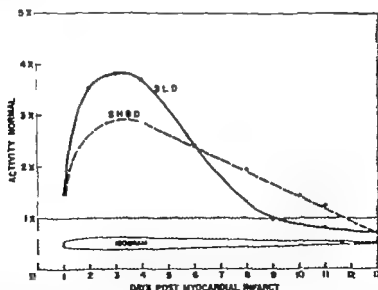


Fig. 3 Graphic depiction of serial isoenzymes and SLD and SHBD activities in the serum from a patient manifesting an uncomplicated myocardial infarct. Note the persistence of elevated levels of SHBD and positive isoenzymes after the normalization of SLD.

infarction. Of the five most applicable enzymatic procedures (SGOT, SLD, SLD isoenzymes, SHBD and CPH) for the confirmation of the diagnosis of myocardial infarct the estimations of CPH and the fractionation of SLD isoenzymes enjoy the greatest degrees of specificity and sensitivity.

Specificity and sensitivity notwithstanding the single most important variable in the diagnostic application of the tests is the time of collection of the sample in relation to the clinical history. False negatives are the rare exception if the appropriate test is used in the light of activity spans in serum.

Estimations of CPH are most useful in the acute clinical situations since a rise in its activity may precede that of the other enzymes by 8 hours. All measurements will be positive within 24 to 36 hours after the onset of the infarction. The major significance of estimations of SHBD resides in the fact that its activity persists after other activity levels have returned to normal.

Isoenzyme fractionation and serial estimations of CPH, because of their enhanced discriminatory ability, are superior to all other enzyme tests for purposes of differential diagnosis and prognostic follow up evaluation.

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Appraisal and reappraisal of cardiac therapy

Edited by Arthur C. DeGross and Alan F. Lyon

Antianginal drugs

Part VII Miscellaneous drugs

Solomon Fisch M.D.*

Bronx N. Y.

The number of drugs that have been proposed for the treatment of angina in addition to those already discussed in this series is myriad. Some of them have fallen into disrepute. Others defy rational explanation for their presumed antianginal efficacy.

1 *The non nitrate long acting vasodilators* These include dipyridamole (Persantin) (see AMERICAN HEART JOURNAL 65:423-424 March 1963) prenylamine (Sequantin) and a benzofuran derivative (Amplivix). Only dipyridamole is available in this country. The other two are still experimental in this country but are available for clinical use in Europe. They all share the property of producing coronary vasodilation in experimental animals when given parenterally. Most of the studies which report favorable results with these agents have been uncontrolled. In controlled experimental work it has been found that when given orally they are devoid of antianginal efficacy when compared with placebo. Accordingly, none of these agents can be recommended for use in angina pectoris.

2 *Psychotropic agents* Besides the barbiturates like phenobarbital or Butisol, other agents such as chloridazepoxide (Librium) and meprobamate (Equanil or Miltown) have been advocated for use in angina pectoris. It has not been proved

that patients with angina pectoris suffer from more anxiety than a comparable population which does not have angina pectoris. It has been conjectured however that when anxiety is present there may be an adverse effect not only on angina pectoris but on arteriosclerotic heart disease in general. This has not been proved. No controlled data are available to indicate that these agents have any specific effect on angina pectoris.

3 *Digitalis and diuretics* It has often been observed clinically that when congestive heart failure supervenes angina pectoris decreases. Sir James Mackenzie was the first to call this to the attention of the medical profession many years ago. The usual explanation given is that heart failure imposes a restriction on the activity of the patient which in turn decreases the frequency of episodes of angina. These observations are difficult to reconcile with those of other clinical studies in which digitalis has been noted to be effective in the treatment of nocturnal angina. In these cases it seems to be reasonable to assume that digitalis works by decreasing congestive heart failure. Catheterization studies have demonstrated that the pulmonary artery wedge pressure rises during some attacks of angina that is heart failure appears with angina. In general, however, it is thought that digitalis does

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Director, Cardiac Therapy Research Unit, Bronx Veterans Administration Hospital, 130 West 161st Street, Bronx, N. Y. 10468

not have a significant antianginal effect in the usual patient. The use of digitalis as antianginal therapy awaits final assessment by carefully controlled double blind studies.

There are some studies which indicate that diuretics like meralluride (Mercurbydren) or chlorothiazide (Diuril) relieve angina pectoris. It is difficult however to compare a placebo with a potent diuretic without the introduction of bias. Further work is needed with these drugs.

4 *Miscellaneous agents* Alcohol (first advocated by Heberden) quinine anti-coagulants ginseng (Fulvicin and Ginsactin) and antithyroid agents such as imidazole (Tapazole) or propylthiouracil are some among many of a heterogeneous group of drugs reportedly useful in angina

pectoris therapy. That so many agents with such diverse pharmacologic properties have been reported to be of benefit in angina pectoris reinforces the conclusion that placebo reaction in angina pectoris is a formidable and real problem that makes assay of efficacy most difficult. There are no significant well controlled studies that attest to the efficacy of any of the above-mentioned therapies.

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Shock after acute myocardial infarction

It has long been recognized that a number of patients hospitalized for treatment of acute myocardial infarction develop the clinical syndrome of shock. The proportion of patients in whom this complication arises has varied widely in different reported series largely because of varying criteria for the definition of shock. In general when the criteria for selection are stringent the incidence of shock is lower and the fatality higher than when less stringent criteria are used thus the proportion of patients dying from this complication is in relative agreement and constitutes between 11 and 19 per cent of admissions.

Lack of uniformity in the adoption of criteria for the diagnosis of cardiogenic shock has likewise led to conflicting reports on the beneficial effects of various therapeutic procedures notably the infusion of pressor amine substances. It is clear that the level of the arterial blood pressure alone does not always offer a reliable guide to the adequacy of tissue perfusion and hence oxygenation which is the true gas gauge of the shocked state. This is further complicated by the earlier and freer use of pressor amines often given prior to admission of the patient to hospital which may prevent the blood pressure from falling to shock levels despite gross depression of the cardiac output and obvious clinical signs of inadequate peripheral blood flow.

Despite numerous clinical and pathologic investigations it is still not clear why certain patients are prone to develop the syndrome of shock after acute myocardial infarction whereas others develop acute left ventricular failure. Neither age or location or extent of the infarction appears to correlate well with the development of shock although it has recently been suggested that death from this complication is less likely to occur in patients with pathologic evidence of remote infarction at autopsy.¹ Still less is known concerning the fundamental pathophysiologic disturbances which lead to the hemodynamic characteristics of shock in man namely hypotension associated with severe depression of the cardiac output. In the past this has led to a polemic in the medical literature on the relative importance of abnormalities of myocardial function (central shock) and of alterations in the control of the peripheral circulation (peripheral circulatory failure). Much of this discussion stemmed from a paucity of data in patients since their precarious condition usually precluded thorough hemodynamic assessment and also from difficulty in obtaining a suitable experimental model for study of the condition in animals. The former difficulty has been overcome by the development of more subtle techniques for the study of the circulation and the latter by

the introduction by Agranoff of a method of reproducing cardiogenic shock in dogs by means of diffuse coronary embolization.

As is so often the case it now seems to be clear that the proponents of both theories concerning the mechanism of cardiogenic shock were in part correct. Although it is true that pressures within the lesser circulation are rarely elevated to levels commonly associated with left ventricular failure, a study of ventricular function in experimental cardiogenic shock in dogs reveals a grossly abnormal relationship between ventricular work and filling pressure. Teleologically it would appear to be desirable that the organism maintain a relatively low left ventricular end diastolic pressure rather than risk the development of pulmonary edema in order to gain a small increase in ventricular work. The mechanism whereby venous return is adjusted to prevent further increase in pressures within the lesser circulation is unknown but the demonstration by Salisbury that sudden distention of the left atricle causes reflex pooling of blood in the capacitance vessels suggests a possible mechanism in man. The apparent paradox in the hemodynamic disturbance in these patients might best be described as *masked left ventricular failure*.

Bearing in mind these pathophysiologic changes we can define the objectives to be sought in treating this condition. These are first to restore and maintain an adequate arterial pressure and second to effect an optimum improvement in ventricular function. The first of these objectives is generally regarded as taking precedence in the belief that maintenance of an adequate perfusion pressure to the brain kidneys and the heart itself is of prime importance. For this reason intravenous norepinephrine a drug with strong vasoconstrictor properties has been most frequently employed in treating this condition in recent years. Although many investigators have reported a reduction in mortality in patients treated with this agent others have noted no significant difference between treated and untreated groups.² When cardiac output has been determined in severely shocked patients it has almost always been reduced out of proportion to the reduction in mean arterial pressure thus calculated total peripheral resistance has been high. Restoration of the patient to toward normal must therefore presuppose a fall in total peripheral resistance and the rationale for employment of a drug with strong vasoconstrictive properties has been questioned.³ It would appear to be logical to place priority on

effecting an optimum increase in myocardial contractility while ensuring an adequate venous return so that arterial blood pressure may be raised by means of increasing cardiac output. This reasoning has led some investigators to suggest that inotropic agents such as the digitalis glycosides which are largely devoid of peripheral vasoconstrictor effect should first be employed. In experimental cardiogenic shock rapid digitalization has proved to be superior to the infusion of norepinephrine in terms of raising the cardiac output without further increasing the left ventricular end-diastolic pressure. The hazard of digitalis excess must be carefully considered but the frequency of digitalis induced arrhythmias after acute myocardial infarction appears to be no greater than in other cardiac emergencies requiring its use.

It would seem to be dangerous to attempt to generalize in recommending any specific therapy in the treatment of cardiogenic shock. Ideally these patients should be cared for in a special treatment area with appropriate facilities for measuring all aspects of circulatory function. The placement of catheters in the superior vena cava and radial artery permit the monitoring of central venous and arterial blood pressures as well as the rapid estimation of cardiac output by the indicator-dilution method. In this way the hemodynamic effect of any specific therapeutic measure can be rapidly assessed. It should be emphasized that general measures in the deeply shocked patient are equally as important as the choice of a specific therapeutic agent. Electrolyte disturbances, acidosis and arterial hypoxatemia should be quickly recognized and corrected. Electrocardiographic monitoring with appropriate control of cardiac arrhythmias should they develop is essential to the total management of these critically

ill patients. No doubt when more data appear from intensive care areas such as the one described a clearer understanding will emerge of the therapeutic rationale in the serious complication of acute myocardial infarction which now claims such an alarming mortality.

R F P Cross MD FRCP(C)
Assistant Prof of Medicine and Physiology
McGill University
Montreal Que Canada

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Transvenous pacing of the phrenic nerves

In September 1964 this group observed that the right phrenic nerve could be stimulated from the superior vena cava. In a patient undergoing transvenous right ventricular pacing with an external pulse generator cardiac respiration ceased and rhythmic contractions of the upper abdominal muscles developed simultaneously. Physical examination revealed a rate of 47 and a pacemaker rate coincident with the abdominal contractions of 72. The ECG demonstrated 2:1 heart block with no response to the regularly timed pacemaker impulses. The subcutaneous catheter returned on surface had been extruded and the tip of the catheter had been displaced proximally to the mid superior vena cava. Fluoroscopically the right diaphragmatic leaf showed rhythmic contraction coincident with

the pacemaker impulse which ceased when the pacemaker was turned off and did not resume when cardiac pacing was reinitiated from the right ventricle.

Since this time the right diaphragm of 10 dogs and 10 patients has been paced. In acute experiments by 2 msec cardiac pacemaker impulses applied to the mid superior vena cava. Regular pacemaker contractions were secured at rates ranging from 45 to 70 per minute and currents ranging from 3 to 12 milliamperes with immediate return to normal expiration when pacing was discontinued. Cardiac action was not disturbed by these activities.

Exploration of a transvenous approach to the left phrenic nerve is now under way. One patient has responded to cardiac stimulatory impulses administered to the left phrenic nerve through the main pulmonary artery. Several others however

Table II Over all comparison Q R and S versus 10-40-60 msec vectors

Vectors	Angles			Voltages		
	Normal FD curves	Smaller range	Less variance	Normal FD curves	Smaller range	Smaller coefficient of variation
Q R and S	9	7	8	7	5	6
10-40-60 msec	4	2	1	8	7	5

*Three sign from at $p < 0.05$ greater

Table I compares mean (M), standard deviation (SD), range (R) and coefficient of variation (CV) or variance ratio (F) for paired sets of data. Range is the crudest of the tests since it does not reflect the frequency of observations at each value. It has been calculated for 96 per cent of observations by eliminating the single highest and lowest measurements. This should approximate $M \pm 2SD$ if distribution is normal. Its unit is degrees (angles) or millivolts (voltage) and represents the difference between the highest and lowest of 48 observations. F (larger SD^2 /smaller SD^2) a two-tailed test of variance is appropriate to compare the distribution of angular measurements since only the scatter about the mean is of interest and the values for M and SD are correlated. F is not suitable however for the voltage comparisons since values for M and SD are related (larger M tend to have larger SD). CV is used because it takes this into account. A normality of frequency distribution (Levene's and kurtosis) was tested at the 0.5% level of significance by Snedecor method. Most of the calculations were performed by computer programs on the IBM 1670.

Table II indicates over all comparison of the two methods with data for M vector excluded. The number of angular measurements which generated normal frequency distribution curves, smaller ranges and less variance distinctly favors the morphologically identified vectors. Comparison of Q and R angles with those of 10 and 40 msec vectors respectively favors the former although only one of six M values reaches a level of significance. The S vector angle was also more stable than the 60 msec vector in all except the frontal plane where both showed a very small scatter. The values for the M vector angles scatter more widely than those of either the R or 40 msec vectors. Differences in the voltage measurements however are not impressive. Those for the Q 10 msec vector pair are very similar but CVs are slightly smaller for the timed vector in all four. CVs for the R and S voltage however are smaller than those of their sister part in six of the seven instances in which they differed.

In conclusion it appears that morphologically defined vectors Q, R and S can be identified with acceptable consistency in normal loops and when

compared to consecutive timed vectors at 10-40 and 60 msec satisfactory ranges of angles and voltages are evident. Their angular positions were somewhat more stable than those of the timed vectors whereas scatter of values for voltage was approximately similar. The position of the M (maximum) vector in each plane was less predictable than that of either of the other two mid loop vectors (I and 40 msec) but its voltage range was equally as acceptable.

I. Calton, William M.D.
Division of Cardiology
Medical College of Georgia
Augusta, Ga. 30902

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Practical remarks on the McFee and Parungao VCG lead system

There is no intention here of debating at length the superiority of the different systems of lead proposed for electrocardiography. However one must stress the fact that an increasing number of investigators give preference to so-called orthogonalized systems of lead based on the lead field concept and using multiple electrodes to neutralize proximity effects. Among such systems the ones of Schmitt¹ of Frank² and of McFee and Parungao³ are well known. They are in fairly good agreement with regard to the wave forms of the VCG tracings that they provide. We now have 3 years of personal experience with the McFee system. In a series of 15 cases both normal and abnormal comparisons between the Frank and the McFee method gave us results that were sufficiently equal so that we could adopt without mental reservation either the one or the other provided that the electrodes are placed precisely. However we adopted the McFee system and this for additional reasons which are mentioned below.

One remark in McFee's original paper³ with regard to comparison between Frank and their own procedure concerned us of the greater reliability of the latter method for routine clinical use. It deals with the variations in the location of the electrodes and their consequences on the reproducibility of the tracings in each system. Inaccuracy or error in the location of anterior or lateral thoracic electrodes prove to be less disadvantageous when the McFee rather than the Frank system is used. This tendency to more distortion with a similar amount of original error in electrode placement seemed to us to be of decisive importance in clinical application. The evidence of less error with the McFee system for the same degree of precision in the application of the electrodes to the skin probably is due to the fact that the frontal bipolar electrodes of the McFee system and the left lateral bipolar electrodes as well cover a relatively larger vertical field distance along the roughly cylindrical surface of the thorax.

Thus a longitudinal displacement has fewer consequences when the McFee electrodes are used than when all electrodes as in Frank's system correspond to one single level. We have also tested in another way the limits of reliability of the McFee triple frontal electrodes with 3 units 20 mm in diameter located at the 3 corners of an equilateral triangle having a side of 60 mm. By comparing two horizontal vectorcardiograms obtained according to McFee one normally executed with the base of the triangle parallel to the transverse axis of the trunk and one after rotation of the triangle by 60 degrees we found striking similarities and sometimes almost an equality of both figures in most of the components. 15 such experiments have been performed. The entirely different positioning of the 3 chest electrodes after a rotation of 60 degrees demonstrates

the validity of the lead field concept in this particular case and represents a simple solution to the problem of using semidirect chest lead points to obtain an average lead largely suppressing proximity effects. We often took advantage of this winning trick on the occasion of VCG demonstrations to visitors and it never failed to persuade them of the astonishing validity of the principle.

McFee and Parungao when presenting their new system of lead in this journal 4 years ago emphasized its suitability for routine clinical application. They said that Frank's or Schmitt's systems in spite of their sound theoretical basis do not strike the optimum balance between accuracy and simplicity. They presented their new system of lead as an improvement in this balance. Our present opinion on the matter would be in agreement with their wish with one reservation that is not to use 8 separate section electrodes as against Frank's 7 but instead to substitute for them plates of grouped electrodes according to the description which follows. For reasons and quite intelligible reasons 9 section electrodes are very difficult to handle because of the need for their precise location on the chest according to an equilateral triangle of accurate dimensions and their precise linear lateral location as well this process implies the use of a special template which is unsuitable for a rapid application. This difficulty doubtless is the reason that this attractive system of VCG lead so thoroughly tested by its authors has not yet received the wide attention that it deserves according to our own experience.

By making a few practical changes we have greatly improved the routine application of the McFee system. These changes consist first in the maintenance in solid dependency of the three frontal wire electrodes 104 mm apart (= 60 mm radius) on a circular Plexiglas plate 15 cm in diameter and secondly application of the same system to the two lateral electrodes on a 110 mm part on a distinct Plexiglas plate. The latter is 14 cm long and narrow with a flat triangular shape (top triangle dimension 5 cm) to allow the addition of third foot at mid-distance of the electrodes and within 2 cm parallel of their line of junction. This third foot is a 20-mm long Plexiglas under the role of which is to mount the whole surface of the plate parallel to the skin (see Fig. 1).

After careful determination and marking of the center points of the mount position both electrode assemblies tripolar and bipolar are easily fixed at the right place by the pressure of a rubber belt around the thorax. Placing the metal electrodes with an adequate electrode jelly is then performed by forcing a finger tip smeared with paste below each unit. It is perhaps necessary to mention on that previous to the skin should be energetically rubbed with an alcoholized pad at all level of application of electrodes. The same process is used for all four



Fig 1

other metal plate electrodes 6 by 3 cm placed on the right axilla, back, left neck, and left thigh according to the McFee description.

Each electrode assembly has a central terminal incorporated into the Plexiglas plate so that only one connection to the amplifiers for each is necessary. The resistances for these two small central terminals are respectively 100,000 and 66,000 ohms as suggested by the authors of the system. This grouping of 3 and 2 units of electrodes effectively reduces to 6 the total number of electrodes in the system. The regularity of the frontal triangle and its correct spacing as well as for the bipolar plate electrode are guaranteed in all cases. The quality of skin resistance and contact are brought to their best very simply. The pressure of the left plays its part in assuring correct placement and contact. At the same time it helps to hold firmly the two other contacts on the right axilla and on the back. The lateral neck electrode is best affixed by the pressing action of a small sandbag 20 cm long and 6 cm in diameter.

Some details related to this grouping of electrodes deserve description. The first is concerned with the possibility of individually leveling each of the small silver unitary electrodes from their mounting points on the circular and on the recto-triangular Plexiglas plates. The object is to place them parallel to the surface of the skin, the inclination of which varies at each level and with each patient. For that purpose each little circular unit electrode is fitted with a central stud 6 mm long and 5 mm in diameter. This stud is forced into a cylindrical tube of flexible plastic material 10 mm long which itself is gently

plugged into a second stud fixed in the Plexiglas table. The ability to bend the mounted electrode with the finger permits all kinds of orientation of its flat surface with angles up to a maximum of 25 degrees. This procedure is easily executed once the tripolar and bipolar Plexiglas plates are inserted under the belt. In practice it is a self-leveling manipulation that adjusts itself as the plate is applied to each electrode.

The second detail is concerned with the possibility of various spacings of the poles of the tripole or double electrodes for a more proportionate adaptation to the body size in younger individuals. For that purpose both of our Plexiglas plates are equipped with a second set of studs having a closer spacing of 45 mm radius for the tripolar and 40 mm for the bipolar. The electrodes and their corresponding plastic tubes are pulled out from the outside studs and plugged into the inside ones. For small infants or babies we have a second and third set of tripolar and bipolar electrode assemblies with radii of 40 and 30 mm respectively.

This system of grouped electrodes has shown itself to be beneficial in every respect and results. I thus consider that the McFee and Parungao VCG method may compete successfully with all other sophisticated systems of clinical electrocardiography now available. It has become a 6 electrode VCG corrected system among the least time consuming for application and most reliable according to the lead field concept.

Thus we hope to have given still more validity to the words of the authors when they state that the object of their system is to maximize accuracy and minimize complexity. By a most agreeable coincidence our modified version of the McFee system has been examined by Dr. McFee himself who happened to visit me at the time of preparation of this annotation. He states that he highly favors our method and intends to adopt it for use in his own laboratory.

Pierre H. Duchesne, M.D.
Professor of Medicine
With technical assistance of
Rajmond Pasche
Geneva University
Geneva, Switzerland

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Address: 26 Boulevard des Philosophes, Geneva. Switzerland.

Book reviews

THE FETUS AND THE NEWBORN. RECENT RESEARCH
British Medical Bulletin Vol 22 No 1 January
1966 Edited by H. W. Cross and G. S. Dawes
London 1966 Medical Department British Coun-
cil 107 pages Price 3s

The *British Medical Bulletin* continues to publish excellent series. This one is no exception. The authors are expert in their fields and most of them are actively engaged in research in the problems that they summarize. Among the subjects presented are morphometry of human placenta, maintenance of isolated fetus, fetal growth retardation, immunity in fetus and newborn, biochemical aspects of newborn liver re-vascularization of the newborn infant and brown adipose tissue as well as other equally important and interesting subjects. This issue is highly recommended. It is authoritative, concise and well written.

HEART AUSCULTATION By Rudolf Zerkermann ed 2
Leipzig 1965 Georg Thieme 535 pages 141 illus
in books

The second enlarged edition of Zerkermann's book has appeared two years after the first edition which is evidence of its favorable acceptance. The volume is comprehensive and up to date. After discussion of the technique of auscultation of the relationship of normal heart sounds to other events in the cardiac cycle and of their mechanism and normal standards (pp. 1-74) murmurs are described with a discussion of their underlying mechanism and their changes with various diagnostic procedures (exercise, Valsalva and Voller maneuvers, vagal stimulation, liver and thorax compression and drug). A table summarizes the effect of phenylephrine, norepinephrine and amyl nitrite on left and right cardiac murmurs in the diagnostic differentiation of various types of valvular heart disease (p. 103). A short chapter (pp. 104-112) is devoted to heart sounds in infants, children and adolescents. The major part of the book (pp. 113-355) is a detailed discussion of heart sounds and murmurs in 124 (?) various pathological conditions with emphasis on differential diagnosis.

Although *Heart Auscultation* is the title of the book, vascular sounds recorded from the neck, head, thorax, abdomen, extremities and ears are also included (pp. 2-6-7-8). The text suffers from a certain lack of uniformity and systematic organization in the actual printing.

The text is illustrated by numerous diagrams which are excellent for teaching purposes. Actual phonocardiograms are shown in the last part

(pp. 331-443). Perhaps by an oversight these phonocardiographic illustrations are not numbered and there are no references in the legends to the text or vice versa. The bibliography (pp. 43-516) is most complete and valuable as assembled by object and alphabetically.

To the knowledge of this reviewer there is no English text which covers the field in the way this monograph does. It is of value to the medical student and resident as a text and to the cardiologist as a reference.

ELECTROCARDIOGRAPHY IN INFANTS AND CHILDREN
Edited by Donald E. Cassle M.D. and Robert F. Ziegler M.D. New York 1966 Grune & Stratton Inc. 366 pages Price \$16.75

This book represents a summary of a symposium sponsored by the American College of Chest Physicians. The participants reviewed some of the important problems in clinical electrocardiography and vectorcardiography. Among the subjects presented in these proceedings are lead systems, relationship of the standard electrocardiogram to the vectorcardiogram, intra-cardiac electrocardiography, the normal electrocardiogram of infants and children and the electrocardiogram of arrhythmic disease states such as left ventricular hypertrophy, a few congenital defects and myocarditis. This book should interest cardiologists, internists and pediatricians but should be of particular value to pediatric cardiologists.

ADVANCES IN CARDIORESPIRATORY DISEASES Vol III
Edited by Andrew L. Benay M.D. F.C.C.P. and Burgess L. Gordon M.D. F.C.C.P. Chicago 1966 Year Book Medical Publishers Inc. 348 pages Price \$11.50

This volume is a composite of 19 lectures from the 1965 series of postgraduate courses of the Council on Postgraduate Medical Education of the American College of Chest Physicians. The papers include such subjects as compartments of lung volume and their physiologic significance, pneumometry, respiratory acidosis, pulmonary edema, cystic fibrosis of the pancreas, metastatic tumors of the lung, amputation bedside diagnosis of arrhythmias and others. All papers are presented in the style of review lectures. This book should be of some interest to students and physicians. Those who read the journals regularly will find little if anything new in this series of lectures.

PROCEEDINGS OF THE NATIONAL STROKE CONGRESS
 Edited by Ralph I. DeLoraine M.D. Springfield
 Ill. 1966 Charles C. Thomas. 214 pages. Price
 \$7.50

This is the proceedings of a congress sponsored by the American Heart Association, the American Medical Association, the Heart Disease Control Program of the United States Public Health Service and the Vocational and Rehabilitation Administration of the United States Department of Health, Education and Welfare. The sessions were conducted in Chicago during October 1964. This summary of the presentation represents the contributions of many people. Sections of the book include discussions of the problems of strokes and their prevention, early care of the stroke patients, consequences and rehabilitation of the patient. There were meetings for the general public and a discussion of community programs. It is good to have the proceedings of such a meeting available for those who are interested but it is unlikely that physicians in practice or students in general will find this book of much value. It is traditional for such meeting little if anything new or unpub-

lished was presented. Meetings of this sort probably are of value although this point of view is debatable especially in view of the fact that because so many similar meetings are held under so many different titles and circumstances the material presented is always extremely repetitious.

Books received

FIVE CONGENITAL CARDIAC DEFECTS: A STUDY OF THE EPIDEMIOLOGY AND NATURAL HISTORY. American Heart Association Monograph No. 53, edited by James W. DuShane and William H. Wenderson. New York, 1966. American Heart Association. 52 pages. Price \$2.50.

YOUR WONDERFUL BABY. By William J. Potts. Chicago, 1966. Rand McNally & Co. 303 pages. Price \$4.95.

Announcements

Under the title of HYDRAULICS FROM THE MEMOIRS OF LEONARD DA VINCI the *Revue Blanche* journal of the Société Hydrotechnique de France is publishing in full the papers read at the first symposium on Cardiac Counterpulsation held in Paris on Nov. 18 and 19, 1965.

In the course of the symposium which was attended by doctors physicians, cardiovascular surgeons and physicists in fluid mechanics such problems as the physiology of cardiac deficiency, arterial pulsation, counterpulsation, aortic techniques bypassing the left side of the heart etc. were discussed.

Orders for this special number should be sent

direct to the Société Hydrotechnique, Boite Postale 41, Grenoble, France.

The New York Academy of Science CONFERENCE ON ARTIFICIAL HEARTS: RECENT ADVANCES will be held at the Waldorf Astoria Hotel, New York City on Nov. 1-2, 1966. The Conference Chairman is Henry Haimovici, M.D., 862 Park Ave., New York, N.Y. 10021.

Invitations to attend the Conference may be obtained by writing to Executive Director, The New York Academy of Sciences, 2 East 63rd St., New York, N.Y. 10021.

Obituary

Samuel Albert Levine

An inspired teacher has left us a pioneer in the diagnosis and treatment of heart disease. The influence of Sam Levine on the lives of his contemporaries and of his host of students in this country and abroad promoted the new science of cardiology to take its place in the very forefront of all the specialties not only of internal medicine but also of surgery in both of which broader fields he kept an active interest all through his life. But it was his vibrant spirit more than what he did and taught that appealed at once to all with whom he came in contact—physicians, patients and friends alike—and will never be forgotten.

Born in Poland, Sam was brought to this country at the age of 3 years. He was a brilliant scholar throughout his schooling while helping to earn his way through secondary schools, Harvard College (A.B. 1911) and Harvard Medical School (M.D. 1914) by working as a newsboy, which elevated the prestige of that job as street car conductor, as waiter and as tutor.

Trained at the Peter Bent Brigham Hospital where he was a long time disciple and friend of Henry Christian, he became an eminent teacher at the Harvard Medical School where he achieved his professorship in 1948 as Clinical Professor of Medicine from which post he retired in 1957.

He carried on postgraduate teaching in classes at the Brigham Hospital for over 30 years and many of the graduate students who took those courses are actively at work in cardiology all over this country and abroad today. During the First World War he served with Thomas Lewis' group at the Heart Hospital at Colchester in England with other American and British physicians. He was pre-eminent in all



18 4 B m

Samuel Albert Levine 1891-1966

three medical careers possible during the last generation: namely, practice, teaching and research. A professorship in cardiology was established in his name at Harvard University by a patient and former Dean C. Sidney Burwell, became its first incumbent.

Sam wrote several books; particularly his pioneer monograph *Coronary Thrombosis: Its Various Clinical Features* which appeared in the journal *Medicine* in 1929.

After James Herrick, who published his

famous clinical introduction to coronary thrombosis in 1912. Sam was the next to recognize this disease. This he did in a famous paper in 1918 based on two cases with differential diagnosis between acute cholecystitis and acute coronary thrombosis (*American Journal of the Medical Sciences* 155:27). Other books included his *Clinical Heart Disease* published in 1936 followed by four more editions and a later book entitled *Clinical Auscultation of the Heart* which appeared in 1949 written in collaboration with one of his most illustrious pupils Dr W. Proctor Harvey of Georgetown University. Many useful papers also came from his pen.

His devoted family consisted of his wife Rosalind, his son Herbert, Chief of Cardiology at the New England Medical Center, and two daughters, Carol, wife of Dr William B. Schwartz, eminent medical investigator also at the New England Medical Center, and Joan, wife of Simon Scheff, attorney.

Sam was a member of the leading medical and cardiological societies of this and foreign countries, but most of all, as I myself can testify, after a companionship of 50 years, Sam was an inspiration to us all.

*Paul D. White, M.D.
Brookline, Mass.*

Editorial

The second sound in the pulmonary area

Aubrey Leatham F.R.C.P.*
London, England

Accurate analysis of the second heart sound is the first requirement for modern auscultation of the heart. It still does not seem to be generally appreciated by many practicing physicians that the second sound in the pulmonary area of normal subjects is composed of both aortic and pulmonary components; indeed even in the pulmonary area aortic closure (A_2) is usually louder than pulmonary closure (P_2) and separation of the two components during the inspiratory phase of breathing is necessary before intelligent observations can be made about A_2 and P_2 . Thus the common expression " A_2 is greater than P_2 " when one is referring to areas has little significance and usually implies a remarkable ignorance of auscultation which became widespread between the First and Second World Wars. Potain¹ knew in 1866 that the second sound reduplicated during the inspiratory phase of continuous respiration. The mechanism of inspiratory splitting is of great interest and is due simply to the fact that the negative intrathoracic pressure of inspiration draws blood immediately into the right heart from its extrathoracic venous reservoir but not immediately into the left since the negative pressure will influence all extrathoracic chambers and vessels equally and will thus

have little or no direct effect on the flow of blood from pulmonary veins to left heart.² The increase in stroke volume of the right ventricle on inspiration results in prolongation of right ventricular systole and delay in P_2 a few seconds later this increase in the volume of blood reaches the left heart and results in a slight increase in stroke volume of the left ventricle and delay in A_2 although this is much less than on the right side since the change is damped by its passage through the lungs. During the inspiratory phase of continuous respiration at usual rates in normal subjects A_2 is at its earliest when P_2 is at its latest, thus resulting in wide splitting of the second sound which may reach 0.1 second. In the expiratory phase however A_2 and P_2 are normally nearly fused and clear separation persisting with slower deeper respiration is almost invariably abnormal indicating that A_2 is early or more commonly that P_2 is late (e.g. right bundle branch block, left to right shunting, atrial septal defect increasing the stroke volume of the right ventricle or pulmonary stenosis). A_2 may be late from prolongation of left ventricular systole (e.g. left bundle branch block or aortic stenosis) and will cause reversal of the order of valve closure in expiration; P_2 will precede A_2 usually

causing audible splitting which will (para-
doxically) disappear during inspiration.^{4,7}

More or less fixed splitting of the sec-
ond sound occurs if the right ventricle is
unable to vary its stroke volume as hap-
pens with failure. If both A_2 and P_2 delay
equally during inspiration (simultaneous
prolongation of right and left ventricular
systole) splitting of the second sound will
also appear to be fixed. This usually indi-
cates an interatrial communication for in-
spiration here instantaneously increases
the filling of both the right and left sides
of the heart; it is a particularly obvious
physical sign since A_2 and P_2 are also
clearly separated and easily heard because
the ejection systolic murmur finishes before
both components.

It has already been stressed that the
second sound in the pulmonary area in
normal subjects is composed of both aortic
and pulmonary components. P_2 is much
softer than A_2 and may be heard in the
aortic area and at the lower left sternal
edge but is not normally transmitted to
the mitral area where A_2 alone is heard.
It may be heard in the mitral area if
auscultated from pulmonary hypertension
or if the underlying ventricle is the right

one as in atrial septal defect so that the
presence of two components of the second
sound in the mitral area is almost invari-
ably abnormal.

Once A_2 and P_2 have been heard other
sounds in late systole and diastole can be
identified and the timing of murmurs de-
coded and thus the second heart sound may
well be considered to be the key to auscultation of the heart.⁸

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Clinical communications

Arrhythmias and potassium in man

Alfred Pick M.D.*
Chicago III

The purpose of this presentation is to review systematically and to illustrate the various disorders of cardiac rhythm induced by or related to abnormal levels of potassium as observed in clinical routine electrocardiography. Accordingly the discussion will be limited to the analysis of mechanisms of arrhythmias without any attempt to correlate them with known bioelectric events at the cell membrane.¹ To this end it is feasible to separate fairly well the disorders of cardiac impulse formation and propagation under the effect of an excess of potassium on the one hand from those associated with a depletion of potassium on the other.

Hyperkalemia

What unchecked and progressive hyperkalemia can do to the cardiac mechanism is illustrated in Fig. 1 which shows serial records from a 63 year old hypertensive and diabetic woman. A pre-existent pattern of left ventricular hypertrophy (Dec. 30, 1947) is on January 17 modified by uremic contour alterations—a prolonged QT interval and pointed T waves—while the sinus rhythm is unaffected. On the next day as potassium toxicity develops all signs of atrial activity have disappeared and a totally irregular ventricular

action becomes progressively slower eventually to cease with a preterminal monophasic deformation of the QRS. The origin of the preterminal ventricular irregular beats is unknown. However recent studies in experimentally produced hyperkalemia using direct records from atria and ventricles² revealed that such beats can be related to continuous sinus impulses blocked from the bulk of the atrial myocardium but conveyed to the ventricles by some preferential path.

Although this type of sinoatrial block may come into operation in the human heart it does not necessarily imply total cessation of atrial conduction. In Fig. 2 the ECG from an infant with tricuspid atresia who developed hyperkalemia reverts during a spell of severe hypoxia with apparent loss of the normal sinus mechanism the atria do respond although only intermittently to impulses of a slowly escaping ectopic center located somewhere in or near the AV junction. Such subsidiary supraventricular centers may be aroused by hypoxic hyperkalemia not only to slow but also to accelerated activity. When this takes place before the development of or without a sinoatrial block the resulting arrhythmia is complete or incomplete AV dissociation. A complex

* From the Department of Cardiology, University of Chicago School of Medicine, Chicago, Ill.
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Address correspondence to: Alfred Pick, M.D., 535 North Dearborn Street, Chicago, Ill. 60610.

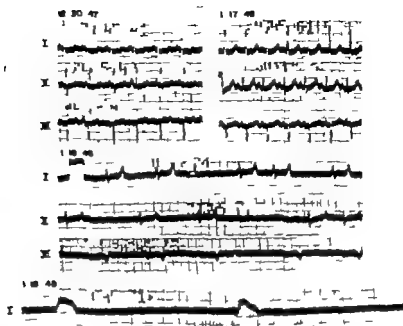


Fig. 1 Electrocardiographic effects of progressive hyperkalemia.

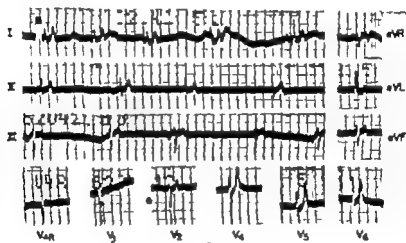


Fig. 2 Irregular escape of low atrial or A-V junctional pacemaker in hyperkalemia.

variety of such a disorder is shown and diagrammatically analyzed in Fig 3 which is the record from a 3¹/₂-month-old cyanotic infant who died after having been removed temporarily from its oxygen tent for recording of the electrocardiogram. The sinus rate has slowed to 50 while the junctional escape rate is speeded up to 77. This fortuitous numerical relationship between the rates of the two pacemakers having a common denominator of 25

results in a peculiar rhythm in which completely or partially conducted sinus impulses appear to be coupled to the ectopic ones. Thus with continued complete ventricular capture as in the upper panel there is a so-called reversed ventricular bigeminy.¹⁰ In the absence of captures concealed penetration of the A-V junction by sinus impulses¹¹ is revealed by the constancy of the interectopic interval as is indicated in the diagram in the lower panel.



Fig. 3. Intra-atrial first-degree AV and intra-ventricular block with runs of ventricular tachycardia in advanced hyperkalemia.

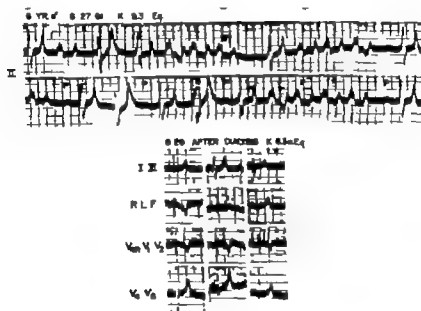


Fig. 4. Incomplete AV dissociation with attempted and completed ventricular captures in hypokalemia.

Enhancement of impulse formation by advanced hyperkalemia may also involve ventricular ectopic centers. Fig. 4 is a record from a 16 year old boy in whom acute renal failure and the associated electrolyte disorders have produced on August 27 marked slowing of the atrial rate but only some of these presumably sinus impulses are conducted. In most of the tracings, there is AV dissociation due to runs of ventricular tachycardia and to single junctional premature beats. The cause of this disturbance of rhythm is revealed by its disappearance on August 28 after partial correction of the hyperkalemia.

A further remarkable feature of the

record at the height of hyperkalemia is generalized slowing of impulse conduction. It is revealed in the atria by the widening of the P waves to 0.24 sec. in the ventricles by the QRS prolongation and peculiar shape of the supraventricular beats and in the AV junction by the prolongation of P-R to 0.40 sec. The intraventricular conduction defect is discussed below (Fig. 59). This record serves to illustrate that in clinical electrocardiography pure hyperkalemia even in its most advanced stages produces no more than a first degree AV block.

When one is dealing with conduction disorders consequent to hyperkalemia some

consideration of the specific type of intra-ventricular block seems to be proper although this does not fall strictly in the realm of cardiac arrhythmias. A classic example is illustrated in Fig 5 which is the record from a 12 year old boy with acute glomerulonephritis. Although leads of the frontal plane suggest a right bundle branch block, this is not borne out by the right precordial leads. The principal involvement of the terminal ventricular depolarization forces by the conduction dis-

turbance has to be attributed to a severe diffuse but correctable peripheral conduction delay involving the free ventricular walls² rather than one or both of the main bundle branches.

If a more typical pattern of bundle branch block is found in hyperkalemic states it can be related to the combination with predominantly unilateral ventricular pathology. Fig 6 shows two records from an infant with transposition of the great vessels, mitral atresia, a diminutive left

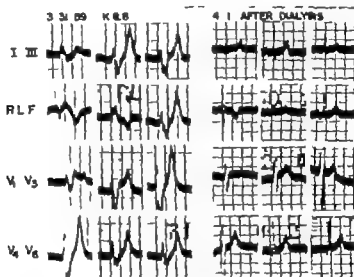


Fig 5 The characteristic intraventricular block of severe hyperkalemia

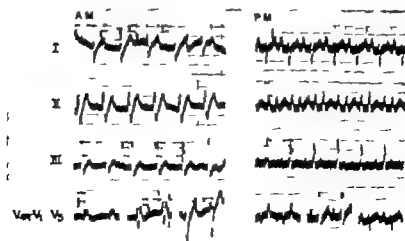


Fig 6 Transient right bundle branch and mural block in hypoxic hyperkalemia

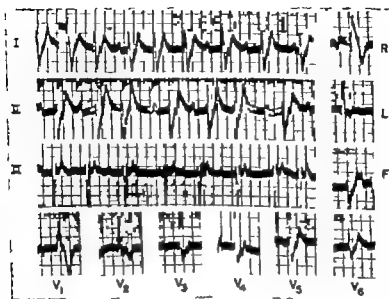


Fig 7 Atrial tachycardia with irregular AV conduction and right bundle branch and mural block due to hyperkalemia in acute cor pulmonale

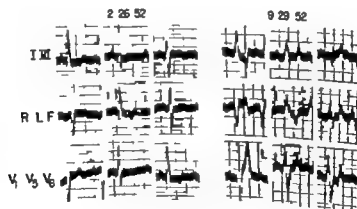


Fig 8 Left-sided intraventricular block in hyperkalemia

ventricle and pulmonary stenosis. In the morning record (AM) taken during a hypoxic spell the typical right bundle branch block pattern appears associated with characteristic hyperkalemic contour alterations. This pattern subsided in the afternoon (PM) to reveal the underlying right ventricular and atrial pathology. A comparable but fatal event is seen in Fig. 7 the record from a 30-year-old woman in who developed extensive atelectasis and an acute cor pulmonale after hysterectomy. A multifocal atrial tachycardia with

irregular AV conduction and the intraventricular block involving the free myocardium as well as the right bundle branch can all be attributed to the combination of hypoxic hyperkalemia with acute dilatation of the right ventricle found at the autopsy.

When hyperpotassemia develops in the presence of left ventricular pathology, the left bundle branch block assumes the appearance of left bundle branch block as is illustrated in Fig. 8 in the case of an elderly man with hypertensive cardiovascular disease.

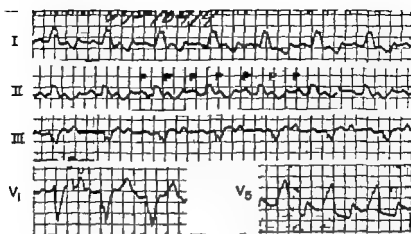


Fig. 9 Intraventricular conduction delay and left-sided intraventricular block in hypoxic hyperkalemia

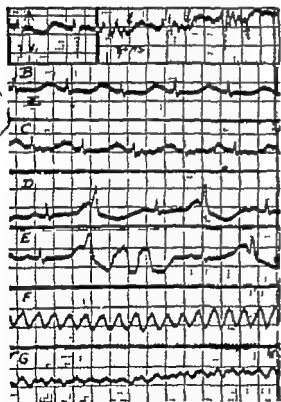


Fig. 10 Ventricular premature beats during the atrial phase in hypokalemia (19-year-old woman, K^+ 2.5 mEq/l.) (from Lipeschkin and Rosenbaum, C. p. 13, Interval of Ventricular Extrasystoles in Relation to the Heart Rate, the U Wave, and the Supernormal Phase of Excitability, Circulation 15:81, 1947, by permission of the American Heart Association, Inc. This record was interpreted according to the authors by Dr. Surawicz.)

emia and a serum potassium of 7.2 mg per cent on September 29. It can be noted that secondary ST-T alterations caused by the intraventricular conduction disturbance are modified but not cancelled by those due to hyperkalemia. Furthermore it can be noted once again that A-V conduction is unaltered despite the high grade hyperkalemia. However this may not be so in the case of hypoxic hyperkalemia. Fig. 9 shows the record from a premature infant in severe respiratory distress. Here the conduction disturbance is general involving the ventricles and the A-V junction the latter in the form of a 2:1 A-V block.

The mechanisms involved in clinical arrhythmias caused by an excess of potassium are summarized in Table I.

Hypokalemia

In contrast to the multiplicity of alterations in origin and propagation of the cardiac impulse which can be related to high levels of potassium in the blood hypokalemia by itself only rarely produces such disorders.¹⁻¹¹ No such case was found in the electrocardiographic files of the Heart Station at Michael Reese Hospital but an observation is on record reproduced in Fig. 10 which shows the development of ventricular fibrillation from premature ventricular complexes occurring on top of large and prolonged T-U deflections—one of the several conditions revealing a vulnerable phase of the human heart.¹² However in recent years ample experience has

Table 1 Mechanisms of clinical arrhythmias caused by an excess of potassium

Pacemaker activity		Impulse conduction
Premus	Slowed	Slowed +++ In the atria and ventricles + In the AV junction
Subsiding	Enhanced in atria and ventricles	+++ When associated with hypoxia

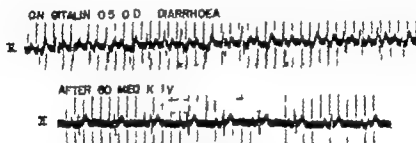


Fig. 11 Ectopic atrial tachycardia with irregular ventricular response, caused by a relative excess of digitalis after depletion of potassium. In the upper panel the dots indicate conducted atrial impulses, the X's blocked ones.

accumulated on the deleterious effects on the cardiac rhythm of a depletion of potassium in conjunction with digitalis medication.

The best known perhaps because of the brand name that has been attached to it is the so-called PVT with block, a typical example of which is shown in Fig. 11. In this 51-year-old man with chronic cardiovascular disease a condition in which this type of arrhythmia is particularly prone to occur, a maintenance dose of digitalis became excessive as a result of an acute loss of potassium induced by diarrhea. The arrhythmia which was promptly corrected by an infusion of potassium is a rapid ectopic atrial rhythm with irregular ventricular response consisting of Wenckebach periods with AV ratios varying between 3 and 4. In Fig. 12 the same type of arrhythmia is illustrated in another digitalized patient. In one case (upper panel) the tachycardia with irregular ventricular response followed the loss of potassium induced by recurrent diarrhea. In the other case (lower panel) the atrial tachycardia with irregular ventricular conduction ratio developed when the hyperkalemia that followed bilateral adrenalectomy

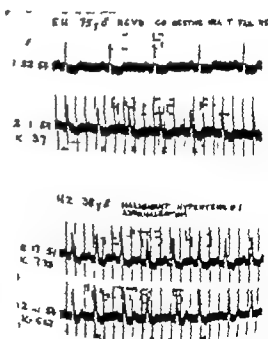


Fig. 12 Atrial tachycardia with irregular ventricular response, due to a relative excess of digitalis in a patient with malignant hypertension.

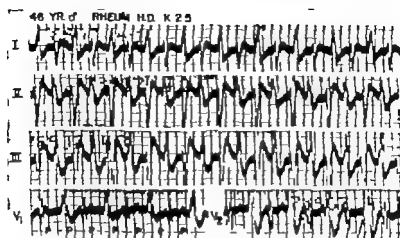


Fig 16 Bidirectional tachycardia (with complete AV dissociation) in hypokalemia

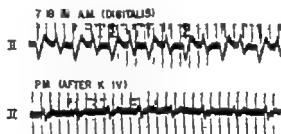


Fig 17 Complete AV dissociation (atrial fibrillation) induced by intravenous AV junctional tachycardia with bidirectional extracellular aberration before the infusion of potassium

vanced hypokalemia could not be corrected and 2 hours later the patient died.

Yet patients with bidirectional tachycardia although in grave danger can be saved if the underlying depletion of potassium is recognized and treated in time (Fig. 17). This case of a 43 year old woman with mitral regurgitation and left bundle branch block also demonstrates that a regular bidirectional tachycardia induced by digitalis in the face of a depletion of potassium indeed originates in AV junctional tissue¹ for complete AV dissociation is seen to persist after partial correction of the deficit in potassium with the atria fibrillating, while the ventricles follow a supraventricular pacemaker at a less rapid rate.

Finally the formation of ventricular ectopic impulses as a manifestation of digitalis toxicity may likewise become apparent after loss of potassium and respond

promptly to the correction of the latter (Fig. 18). This 74 year old man with diffuse ischemic heart disease and old posteroinferior wall infarction developed bigeminy due to single ventricular premature beats which in Lead III multiplied to give rise to a run of bidirectional ventricular tachycardia. In contradistinction to the junctional type it is here attributable to the multifocal formation of impulses in the ventricles because the intervals between the beats are not regular but alternate. However this makes no difference with regard to the beneficial effect of the infusion of potassium.

Our experience concerning the mechanisms of clinical arrhythmias caused by a deficit in potassium are listed in Table II.

Summary

The following conclusions from our observations in clinical electrocardiography

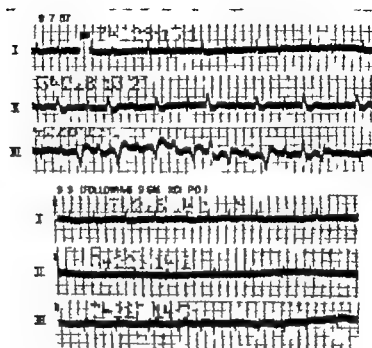


Fig. 15 Bidirectional ventricular tachycardia in trial fibrillation caused by the formation of ectopic impulses and abolished by potassium medication

Table II Mechanisms of clinical arrhythmias caused by a deficit in potassium

Pacemaker activity		Impulse conduction
Without digitalis	Unchanged	Unchanged
With digitalis	Primary Secondary	Unchanged (arrhythmias caused by tachycardia and/or digitalis)
	Unchanged Enhanced in atria, AV junction and ventricles	

can be drawn concerning mechanisms of potassium induced arrhythmias.

1 Under the influence of an excess of potassium the formation of impulses becomes irregular with slowing of the primary pacemaker and acceleration of subsidiary centers. The conduction of impulses is slowed severely in ordinary atrial and ventricular myocardium but only moderately in the specific fibers unless it is aggravated by hypoxia or other associated pathology, especially acute ventricular dilation.

2 A deficit in potassium by itself affects the formation and conduction of normal impulses only exceptionally. However in

digitalized patients the acute depletion of potassium induced by vomiting, diarrhea, diuretic diuresis or endocrine disorder causes an acceleration of the generation of ectopic impulses in the atria, in the AV junction and in the ventricles. Disorders of the conduction of impulses then occur in the AV junction and ventricles but are only secondary because of the accelerated pacemaker rate or the digitalis medication.

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Coronary arteriovenous fistula

Nine operated cases

Shigeru Sakakibara M.D.*

Yasuyoshi Iokoyama M.D.

Akiyoshi Takao M.D.

Mitsuo Negi M.D.

Haruko Gomi M.D.

Tokyo Japan

The discovery of a continuous murmur at an unusual site over the precordium presents an interesting diagnostic problem. Coronary arteriovenous fistula is among the possible causes of such a finding. Coronary arteriovenous fistulas are divided into two major groups on functional grounds.¹ The first group includes anomalies without pulmonary or aortic valvular atresia, and the second group comprises coronary anomalies with pulmonary or aortic valvular atresia characterized by retrograde coronary flow. Main differences in clinical signs and symptoms are observed between these two groups.

Nine operated cases belonging to the first group are reported here, and attention is drawn to the ease of diagnosis as well as surgical treatment.

Case reports

Pertinent findings in the 9 cases from our Institute are shown in Table 1.

1. Clinical findings. There were 5 female and 4 male patients. Subjective symptoms were lacking in all patients except one (Case 8). One patient, an 11-year-old boy

(Case 8) entered the hospital because of intermittent fever, general fatigue, purpura, and pain in the joints for 2 months prior to admission. Five patients (Cases 2, 4, 6, 8, and 9) had a history of recurrent respiratory infection. Systolic blood pressure was normal, however, diastolic blood pressure remained low, especially in 2 patients (Cases 5 and 8) in whom it was 0 mm Hg when estimated by the auscultatory method. The chest film showed moderate to marked cardiomegaly in 6 patients. Peripheral pulmonary vascularity was increased in all except in one patient (Case 3). The aortic knob was prominent in only 2 patients. There were no specific findings in the electrocardiogram. Six patients showed left ventricular overloading. No electrocardiographic abnormalities were found in the others. All 9 patients showed sinus rhythm and a normal P-R interval. Only one patient (Case 2) had S-T depression in the left precordial leads.

The maximum continuous murmur was noticed in the pulmonary area in 2 patients (Cases 1 and 3). In 1958, one patient (Case 1) with a diagnosis of ventri-

*From the Thoracic Unit of Tokyo University Medical College, Tokyo, Japan.

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Address: Heart Unit of Tokyo University Medical College, 1-5-4 Yushima, Bunkyo-ku, Tokyo, Japan.

cular septal defect associated with pulmonary insufficiency underwent surgery the finding at operation was coronary arteriovenous fistula draining into the pulmonary artery. In another patient (Case 3) the preoperative diagnosis was patent ductus arteriosus but since a continuous thrill remained over the pulmonary trunk even after ligation of the patent ductus the pericardium was opened and an anomalous coronary artery communicating with the pulmonary artery was found.

The location of the maximum continuous murmur was noted along the left lower sternal border in 5 patients (Cases 2, 4, 5, 6 and 8). Retrograde aortography revealed an anomalous coronary artery draining into the right ventricle in these cases. In 2 patients (Cases 7 and 9) in whom entry was into the right atrium the maximum point of the continuous murmur was at the second and third right intercostal spaces close to the sternum. In all cases the intensity of the continuous murmur increased toward the second heart sound and then waned. This probably was the reason that the pressure gradient between the aorta and

the right cardiac chambers became much greater around the second heart sound. In Case 9 of the present series a recording of the pressure in the fistula during the operation revealed the highest pressure around the second heart sound. In this series no diastolic accentuation of the murmur was observed even by phonocardiography. The continuous murmur became to and fro in character with systolic accentuation in Case 8 only; this patient had a high right ventricular pressure 95 mm Hg in systole accompanied by bacterial endocarditis.

2. Diagnostic studies. The angiocardiogram was of great value not only in establishing the diagnosis but also in demonstrating anatomic details of the anomalous vessels. We preferred to use selective retrograde aortography, a procedure in which radiopaque material was injected into the base of the aorta through a catheter. The aortograms clearly showed generalized dilatation and tortuosity of the coronary artery bearing the fistula. By this method 7 cases were diagnosed correctly before operation (Fig. 1).

Cardiac catheterization showed an oxygen step up in the chamber bearing the



Fig. 1. Case 6. Anteroposterior (left) and right anterior oblique (right) positions. Dilated coronary arteries drained into the right ventricle through the posterior wall of the heart.

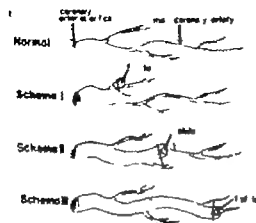


Fig 2 Abnormal vessels were ligated at the sites indicated by the dotted lines. The right coronary artery, the left anterior descending coronary artery and the left circumflex coronary artery were considered to be the main coronary vessel. Scheme I: fistula is found in one of branches of the vessel. Scheme II: fistula is observed at the middle part of the vessel. Scheme III: fistula is located at the end of the main artery.

fistula. The pulmonary arterial pressure was over 60 mm Hg in 3 patients (Cases 2, 5 and 8).

Surgical procedure The abnormal vessel was invariably a part of a normally distributed coronary artery that had branches of normal size beyond the point of the fistula into the right side of the heart. Anomalous coronary arteries were classified into three types (Schemes I, II and III; Fig 2).

Anomalous vessels were ligated as shown in Fig 2. The operative procedure was concerned with division of the affected coronary artery as close as possible to the site of the fistula in order to insure that no collaterals entered below the site of division. In only one patient (Case 4, Scheme III) were mattress sutures placed behind the coronary artery in a manner which would obliterate the fistulous communication without interruption of the continuity of the parent vessel. However, the continuous murmur reappeared approximately 1 month after operation and remained present for as long as 4 years afterward. In the other 9 patients in whom ligation of the abnormal coronary vessel was performed, the continuous murmur disappeared com-

pletely. During the operation, electrocardiographic monitoring was important. Epicardial electrocardiography was considered to be the best way to observe the acute myocardial ischemia and its prompt abatement because the electrocardiogram indicated the local ischemic changes of the myocardium after ligation of the fistula. Our experiences showed that even ligation of a small fistulous artery caused an elevation of the S-T segment in the territory supplied by the vessel. S-T elevations continued from a few minutes to about an hour. Most significant elevations of the S-T segment were noticed in cases belonging to Scheme II (Cases 4 and 5) without any apparent effect on the color or contractility of the heart. Abnormal Q waves did not appear after surgery. All patients were operated upon without the use of extracorporeal circulation or hypothermia. No postoperative complications were noted except for retro sternal abscess in Case 3.

Discussion

Apart from the consideration as to which coronary artery is involved, coronary arteriovenous fistulas are divided into five types according to the chamber or

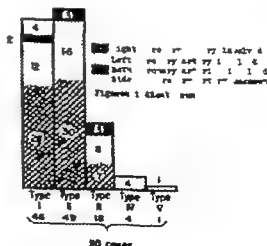


Fig 3 Coronary arteriovenous fistulas without pulmonary or aortic valve atresia were divided into 5 types. Type I: Reference No. 2, 7, 9, 10, 14, 2, 27, 29, 3, 34, 40, 0. Type II: Reference No. 1, 3, 10, 37, 33, 15, 49, 57, 59, 63, 68, 1, 86. Type III: Reference No. 4, 13, 1, 18, 25, 31, 59, 65, 0, 87, 85. Type IV: Reference No. 26, 37, 39, 87. Type V: Reference No. 90.

Table 1. Pertinent findings in 9 cases of coronary arteriovenous fistula

Case No.	Age (yr.)	Sex	Systolic thrill	Continuous murmur	Pulmonic second sound	X-ray findings		
						Heart	Pulmonary congestion	Heart/thorax ratio (%)
1	0	M	—	gr III 2nd LICS	+	Normal	+	54
2	3	F	—	gr IV 4th LICS	++	Normal	++	53
3	3	F	+	gr IV 2nd LICS	Normal	Normal	±	43
4	11	F	La	gr IV 3rd and 4th LICS	++	Small	++	61
5	7	F	Faint	gr IV 4th and 5th LICS	+	Normal	+	51
6	53	M	+	gr IV 3rd and 4th LICS	+	Normal	++	58
7	5	F	—	gr III 2nd and 3rd RICS	Normal	Large	+	50
8	11	M	—	gr III systolic gr I diastolic 3rd LICS	++	Normal	++	60
9	11	M	—	gr III 2nd and 3rd RICS	+	Large	+	55

L/C Left ventricle; L/S Left sternal; R/C Right ventricle; 2nd, 3rd, 4th, 5th, 6th, 7th, 8th, 9th, 10th, 11th, 12th, 13th, 14th, 15th, 16th, 17th, 18th, 19th, 20th, 21st, 22nd, 23rd, 24th, 25th, 26th, 27th, 28th, 29th, 30th, 31st, 32nd, 33rd, 34th, 35th, 36th, 37th, 38th, 39th, 40th, 41st, 42nd, 43rd, 44th, 45th, 46th, 47th, 48th, 49th, 50th, 51st, 52nd, 53rd, 54th, 55th, 56th, 57th, 58th, 59th, 60th, 61st, 62nd, 63rd, 64th, 65th, 66th, 67th, 68th, 69th, 70th, 71st, 72nd, 73rd, 74th, 75th, 76th, 77th, 78th, 79th, 80th, 81st, 82nd, 83rd, 84th, 85th, 86th, 87th, 88th, 89th, 90th, 91st, 92nd, 93rd, 94th, 95th, 96th, 97th, 98th, 99th, 100th. Left ventricle

vessel into which they drain (Fig. 3). Type I—draining into the right atrium. Type II—draining into the right ventricle. Type III—draining into the pulmonary artery. Type IV—draining into the left atrium. Type V—draining into the left ventricle.

Of the total of 118 reported cases of this anomaly which have been collected from the world literature including 9 cases of our own, there were 49 of fistulous communication with the right ventricle and 46 of fistulous drainage into the right atrium. The right coronary artery is more frequently involved than the left. In 8 cases^{1,11,12,14,15} including our Case 6 both coronary arteries participated in the fistula. The association of patent ductus arteriosus with coronary arteriovenous fistula has been documented in 5 cases^{1,2,11,12} including our Case 3. In Fig. 3 we did not include the following: Jacobs's case¹⁶ and Brown's case¹⁷ (these were considered to be cases of ruptured sinus of Valsalva); Gross's case¹⁸ (the anomaly was not clearly described) and the last 3 of the 7 cases recently reported by Bjork¹⁹ (these were considered

to be cases of atypical bronchial artery). It was difficult to differentiate coronary arteriovenous fistula of Type III from anomalous origin of the coronary artery or Bland White Garland syndrome. Murra's second case²⁰ and Michaud's third case²¹ were considered to be instances of Bland White Garland syndrome.

When the fistula drains into the right atrium (Type I) the continuous murmur is best heard in the second and third right intercostal parasternal areas or it is often clearly audible along the lower right or left sternal border (Fig. 4). When entry is into the right ventricle (Type II) the location of the maximum continuous murmur is noticed at the third, fourth and fifth left intercostal spaces close to or over the sternum and only in a few cases may it be noticed along the right sternal border. When the fistula is in communication with the pulmonary artery (Type III) the maximum point of the murmur is heard at the second or third left intercostal space. By auscultation it would be very difficult to differentiate this Type III from patent ductus arteriosus. There were 4 cases^{11,12,14,15} in the literature in which the left coronary

Electrocardiogram			Systemic blood pressure (mm Hg)	Coronary artery	Anatomic type
QRS axis	Rate in 1 (min)	Interpretation			
+30	40	L.V.H	110/80	Right	Type III Schema I
+90	44	L.V.H	110/40	Left	Type II Schema III
+30	10	\normal	130/40	Right	Type III Schema I
+80	42	L.V.H	120/70	Right	Type II Schema II
+80	62	L.V.H	104/0	Right	Type II Schema II
+45	51	L.V.H	120/30	Both	Type II Schema III
+85	52	\normal	100/40	Right	Type I Schema I
+80	48	L.V.H	104/0	Right	Type II Schema III
+80	19	\normal	120/70	Right	Type I Schema I

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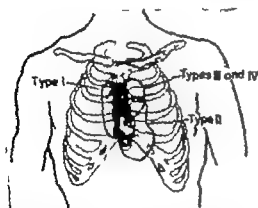


Fig. 4 The location of the maximum intensity of the murmur depends upon the site of the abnormal communication. Its position usually corresponds to the anatomic site of the chamber or vessel participating in the abnormal connection.

artery drained into the left atrium (Type IV). In these cases the maximum continuous murmur was also noticed at the pulmonary area. However one case¹⁰ with the fistula draining into the left ventricle was reported without description of the auscultatory findings.

Certain conditions can cause a continuous murmur to be atypical such as pulmonary hypertension,¹¹ congestive heart failure,¹² atrial fibrillation,¹³ and low aortic diastolic pressure,¹⁴ also a newborn baby¹⁵ shows a soft systolic murmur instead of a continuous murmur.

Gasul and associates¹ pointed out that dilatation of the aorta is common in this anomaly. However we consider that the aortic knob is usually more clearly noticeable in patent ductus arteriosus than in this anomaly. Intracardiac calcification was demonstrated in a case reported by Colbeck and Shaw.¹⁶ There have also been reports of films showing unusual cardiac silhouettes due to aneurysmal dilatation of the coronary artery.¹⁷⁻¹⁹ The dilated coronary artery may be seen as an excrescence on either border of the heart in posteroanterior chest films²⁰⁻²² since the right coronary artery or the circumflex branch of the left coronary artery is most frequently involved.

In 96 of 118 case reports there was electrocardiographic description and in 33 per cent of them (i.e. 36 of 96 cases) the electrocardiographic findings were non-

mal. For 35 of the 46 Type I cases there was an electrocardiographic record. Only 5 of them showed right bundle branch block. In 11 of the 35 cases there was atrial fibrillation and in all 6 cases the patient was over 60 years old.

Retrograde aortography helps in the differentiation of coronary arteriovenous fistula from many other anomalies which produce a continuous murmur over the precordium. This examination is easy to perform but necessary for the diagnosis of this anomaly and should be carried out from two projections in order to show the details of the involved coronary artery.

In infants the main cause of death is congestive heart failure¹⁰ and pneumonia. However beyond infancy congestive heart failure rarely develops but bacterial endocarditis is more frequently experienced as in Case 14.^{11,12,13,14} Congestive heart failure becomes the main cause of death again after 40 or 50 years of age.^{15,16,17,18} It is clear that patients with the Type I fistula easily develop atrial fibrillation which is often followed by congestive heart failure.^{14,15,16} No advantage is to be gained by postponing operative intervention because asymptomatic lesions may eventually lead to bacterial endocarditis or cardiac decompensation.

Severe complications such as cardiac arrest¹ and cardiac failure¹² have been reported to follow the operation but these incidents may not appear to be related to the ligation of the abnormal coronary artery itself. Patients included in Schemata I and III seem to be able to tolerate well the obliteration of the coronary artery. The patients belonging to Schema II suffer mostly from significant myocardial ischemia after operation. We consider however that there is usually enough adequate collateral circulation to allow for division of the affected coronary artery even in cases included in Schema II as observed in our Cases 4 and 5. Thus the surgical technique of preserving the continuity of the abnormal artery instead of ligating it is usually unnecessary although some authors have described successful procedures of obliteration of the fistulous communication without interruption of the continuity of the affected artery.

Some investigators insist that the main

vessel should be ligated at its origin. However dilated coronary arteries are not congenital in origin but are secondary to excessive blood flow so that the ligation should take place at the site of connection to the chamber rather than at the origin of the vessel. Rupture of a dilated coronary artery after operation has not yet been reported. Surgical treatment with complete disappearance of many symptoms was carried out in Case 8 of our series; this patient had bacterial endocarditis and the highest right ventricular pressure of all reported cases. This case demonstrated clearly the effectiveness of surgical closure of the abnormal artery.

Summary

Nine operated cases of coronary arteriovenous fistula were reported with a brief review of the literature. Retrograde aortography is the best diagnostic method although a continuous murmur atypically located for patent ductus arteriosus is suggestive of this anomaly. In view of the relative simplicity of the operation early correction should be made before severe complications appear.

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The isoenzymes of lactic dehydrogenase

1 Myocardial infarction and coronary insufficiency

Donald O. Muller MD

Helson P. Truglia MD

John W. Evans MD*

Washington D C

Lactic dehydrogenase (LDH) is present in man as five heterogeneous isoenzymes. Each isoenzyme molecule contains four subunits which are of two basic types: the M or muscle/liver unit and the H or heart unit.¹ LDH₁ and LDH₂ are homogeneous, containing four M and four H units respectively, whereas LDH₃, LDH₄, and LDH₅ are combinations of the two basic subunits. The isoenzymes can be identified by differences in electrophoretic mobility, heat stability, and reaction rates with varied substrates and coenzymes.

Wroblewski and Gregory² have shown that heart muscle and erythrocytes contain large amounts of LDH. The LDH present in liver and skeletal muscles is largely LDH₁, LDH₂, LDH₃, and LDH₄, are distributed widely and in variable amounts in heart muscle, reticuloendothelial lung, and other tissues. The five isoenzymes are present in the serum of normal human beings in the following relative concentration: LDH₁ > LDH₂ > LDH₃ > LDH₄ > LDH₅. The clinical applications of determining serum LDH

isoenzyme activity are based on the assumption that this activity reflects in part the release of isoenzymes from tissues damaged by a specific disorder.³

A prospective study of LDH isoenzyme activity was conducted in patients with myocardial infarction, coronary insufficiency, pulmonary embolism, and a variety of other acute medical and surgical conditions. This paper presents the results in patients with acute myocardial infarction and acute coronary insufficiency.

Material and methods

Thirty normal subjects (16 men and 14 women ranging in age from 21 to 61 years; mean age of 31 years) served as controls. Six other subjects were sampled daily for 5 days to determine individual variability in total LDH and isoenzymes. To test the reproducibility of the method, 20 determinations of total LDH were performed within 2 days on a single specimen of pooled human serum and on a single specimen from a patient with elevated serum total LDH.

Twenty-three patients (19 men and 4

* With Department of Medicine, George Washington University, Howard Hospital and School of Medicine, Washington, D.C.

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Address: Director of Cardiology, George Washington University Hospital, 2200 22nd St. N.W., Washington, D.C. 20037

women) in whom the diagnosis of myocardial infarction was established by the history of acute substernal or precordial chest pain and confirmatory evidence of acute myocardial infarction in serial electrocardiograms (development of Q waves with appropriate changes in the ST segment and T wave) were studied. Subjects in whom the clinical onset was indefinite were excluded.

Four of the 23 patients with myocardial infarction developed transient cardiac decompensation. 3 were hypotensive (clinical shock was present in one); 3 demonstrated a pericardial friction rub during the first postinfarction week and all survived. All patients received Demerol or morphine for pain and 18 were treated with a combination of heparin and Coumadin.

Eighteen patients with coronary insufficiency (13 men and 5 women) were studied. The diagnosis was made on the basis of typical substernal chest pain lasting more than 15 minutes and the appearance of acute myocardial ischemia in serial electrocardiograms. Subjects were excluded when other causes of chest pain were identified during the study.

Seven of the 14 patients with coronary insufficiency gave a history of previous myocardial infarction whereas 5 others had experienced angina pectoris. Eight of the 14 experienced recurrent pain while under study but none developed the abnormal Q waves of myocardial infarction in serial electrocardiograms. Two subjects developed transient cardiac decompensation; none were hypotensive and all survived. Fifteen patients received Demerol or morphine and heparin and Coumadin.

In addition serial determinations of enzyme activity before and during treatment with heparin and Coumadin were performed in 2 control patients without evidence of cardiac, pulmonary or hepatic disease.

The serum activities of glutamic oxaloacetic transaminase (SGOT), glutamic pyruvic transaminase (SGPT), total lactic dehydrogenase (LDH) and LDH isoenzymes 1, 2, 3, 4 combined and 5 (LDH₁, LDH₂, LDH₃) were determined serially from the time of presentation (within 1 to 4 days of clinical onset) for 10 to 14 days. Samples of serum were frozen promptly and the

enzyme determinations were performed in duplicate within 3 days of collection. Hemolyzed sera were discarded. SGOT was determined by the method of Karmen and associates⁶ and SGPT by the method of Wroblewski and LaDue.⁸ Total LDH was determined by the spectrophotometric method of Wroblewski and LaDue.⁸ LDH isoenzymes were separated by differences in heat stability, as described by Plagemann and associates⁷ and determined by the technique used for total LDH.

Serial determinations (every third day or first 4 consecutive days) of bilirubin (method of Milloy and Evelyn⁹), alkaline phosphatase (method of Kline and associates¹⁰) and thymol turbidity (method of Shunk and Horgland¹¹) were performed in all patients. Bromsulphalein (BSP) retention (method of Rosenthal and White¹²) was determined in a few cases.

Results and comment

Normal values. The enzyme data obtained in control subjects are found in Table I. The LDH isoenzymes can be expressed as absolute units or as a percentage of total LDH activity. We have selected the former method to describe the results in this study.

Determinations of the coefficient of variation on the normal pooled serum and on the abnormal serum yielded a reproducibility of 5.6 and 2.3 per cent respectively. Analysis of total LDH and LDH isoenzyme activities performed serially on control subjects showed a maximum daily variation of 60 units and a coefficient of variation for total LDH of 4.3 per cent, for LDH₁ of 5.9 per cent, for LDH₂ of 9.9 per cent and for LDH₃ of 3.0 per cent. These daily variations in LDH activity do not significantly exceed the variations in the reproducibility of the method.

Heparin and Coumadin controls. The administration of these drugs in therapeutic dosage to the 2 control patients did not affect the serum activity of the enzymes. It was also noted that in the subjects with myocardial infarction and coronary insufficiency neither Demerol or morphine nor heparin or Coumadin seemed to influence the isoenzyme activities.

Myocardial infarction. For number of subject the mean values for each enzyme

Table 1 Values for serum enzyme activity from 30 normal control subjects

	Mean	Standard deviation	Range ($\pm 2 S D$)	Per cent total LDH activity	Range per cent ($\pm 2 S D$)
SGOT	71	8.5	10-14	—	—
SGPT	19	6	7-31	—	—
Total LDH	312	49	71-410	—	—
LDH	91	20	31-131	29	1-36
LDH	113	23	8-139	36	18-44
LDH	107	25	17-131	25	7-43

Table II Daily excreted data from 23 patients with acute myocardial infarction

	Day										
	1	2	3	4	5	6	7	8	9	10	11
SGOT											
Subjects	8	16	22	22	23	2	2	22	18	16	12
Abnormal	5	13	17	14	9	8	7	7	3	2	1
Normal	3	3	5	8	1	15	15	15	15	14	11
Mean (±SE)	119	117	83	61	48	48	44	38	37	39	35
SGT											
Subjects	8	16	22	2	23	2	22	22	18	16	12
Abnormal	4	5	8	5	3	5	5	4	3	1	1
Normal	4	11	14	17	20	17	17	18	15	15	11
Mean	35	35	31	30	2	30	27	3	21	20	15
Total LDH											
Subjects	8	18	2	2	23	2		2	18	16	12
Abnormal	5	12	2	22	22	21	10	18	14	12	8
Normal	3	6	0	0	1	1	3	4	4	4	4
Mean	110	100	260	200	988	913	91	683	509	610	463
LDH											
Subjects	8	16	2	2	3	2	2	22	18	16	1
Abnormal	4	19	15	18	11	17	13	13	11	5	4
Normal	3	9	9	4	1	3	9	9	7	11	8
Mean	206	217	234	5	5	193	183	140	123	148	14
LDH											
Subjects	8	1	2	2	23	22	2	2	18	16	1
Abnormal	5	12	20	20	20	18	0	18	10	2	8
Normal	3	4	2	2	1	4		4	8		4
Mean	214	3	39	291	2	36		196	161	17	159
LDH											
Subjects	8	18	2	2	23	2	2	2	18	16	12
Abnormal	5	17	2		2	2	2	21	17	13	10
Normal	3	1	11	0	1	0	1	1	1	1	1
Mean	117	629	692	66	218	487	240	250	286	276	230

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and the number of abnormal enzyme values for each day of the study are reported in Table II. The means of the serial enzyme curves for the subjects with myocardial infarction are illustrated in Fig. 1.

All 23 patients demonstrated an increase in total LDH, LDH₁, LDH₂ and LDH₃. In every case the maximal elevation occurred before the fifth postinfarction day and gradually declined without a secondary elevation. Twenty-one subjects demonstrated a considerably greater increase in

LDH₂ than in LDH₃ or LDH₁, whereas in the other 2 subjects LDH₂ and LDH₃ increased in equal proportion.

The means of the various enzymes demonstrated the following: (1) Total LDH was elevated from day 1 to 11 with a peak value of 1260 units on day 3; (2) LDH₂ was elevated from day 1 to 10 with a peak value of 275 units on day 5; and (3) LDH₃ and LDH₁ were elevated from day 1 to 11 with peak values on day 1 of 374 and 717 units respectively. The

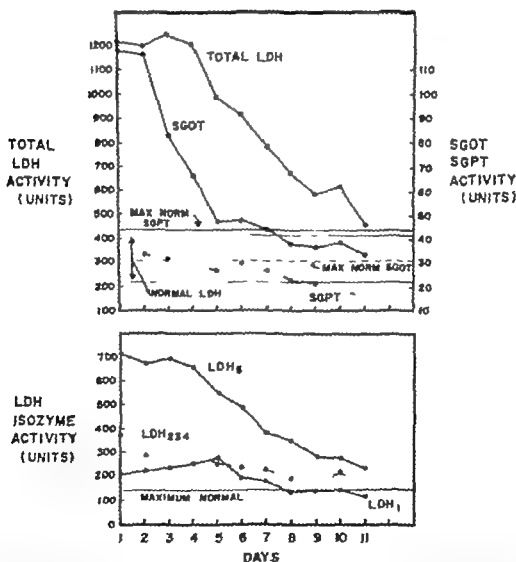


Fig. 1. The mean curves for SGOT, SGPT, total LDH and the LDH isoenzymes 1, 2, 3, 4, 5 from 23 patients with acute myocardial infarction are shown from the first to the eleventh postinfarction day. The normal range for total LDH activity and the upper limit of normal for SGOT, SGPT and the LDH isoenzymes are included for reference.

maximal individual values were 3300 units for total LDH, 800 units for LDH₁, 940 units for LDH₂₊₄ and 1760 units for LDH₅.

SGOT was abnormal in 22 of the 23 patients. An initial peak was observed before day 5 in every case; however in 10 patients a late secondary elevation was also noted (mean peak on day 8). Three of the subjects with secondary elevations had experienced recurrent pain but in the other 7 there was no correlation with clinical events. The secondary elevations in SGOT were not associated with a further rise in total LDH or LDH isoenzyme activity. The group mean for SGOT was elevated on days 1 to 6 with a peak value of 119 units on day 1. The maximum in

dividual value observed was 398 units.

SGPT was abnormal in 13 patients (56 per cent). Peak values occurred before day 5 in 12 instances and 3 of these were associated with later secondary increases. The remaining subject demonstrated a single abnormal elevation after the fifth day. The group mean was elevated on days 1 and 2 with a maximum value of 35 units on day 1. The maximum individual value was 113 units.

Only one of the 23 patients demonstrated significant and persistent abnormalities in liver function. This patient had post necrotic cirrhosis confirmed by liver biopsy, and although the LDH isoenzyme response to myocardial infarction was typical SGOT and SGPT values re-

Table III Daily enzyme data from 18 patients with acute coronary insufficiency*

	Day										
	1	2	3	4	5	6	7	8	9	10	11
SGOT											
Subjects	13	13	16	16	16	15	15	13	10	9	7
Abnormal	3	7	1	0	3	2	2	1	4	1	1
Normal	10	13	15	16	13	12	13	12	6	8	6
Mean (units)	34	31	8	28	32	31	37	32	35	28	33
SGPT											
Subjects	13	15	16	16	15	14	14	12	10	9	7
Abnormal	2	7	1	2	0	0	0	0	0	0	0
Normal	11	13	15	15	15	14	14	12	10	9	7
Mean	24	3	70	13	17	18	18	16	17	15	15
Total LDH											
Subjects	13	15	16	16	16	15	15	13	10	9	7
Abnormal	4	7	4	3	2	7	4	1	3	2	1
Normal	9	8	12	13	14	12	11	12	7	7	6
Mean	401	479	384	354	367	391	389	375	416	391	340
LDH₁											
Subjects	13	15	16	16	16	15	15	13	10	9	7
Abnormal	7		8	7	6	8	5	8	3	1	4
Normal	6	8	8	9	10	7	10	5	5	8	3
Mean	144	158	144	128	133	137	125	140	163	144	129
LDH₂₊₄											
Subjects	13	15	16	16	16	15	15	13	10	9	7
Abnormal	6	9	6	5	8	9	9	5	4	3	2
Normal	7	6	10	11	8	6	6	8	6	6	5
Mean	170	139	176	115	120	120	139	112	144	137	112
LDH₅											
Subjects	13	15	16	16	16	15	15	13	10	9	7
Abnormal	7	4	5	4	3	3	3	1	3	7	1
Normal	6	11	11	12	13	12	12	12	7	2	6
Mean	123	140	139	131	11	120	121	113	124	113	166

* The number of subjects sampled the first 11 days on 1 enzyme activity and 11 on 2 enzymes is 13. 11 subjects re-biased from 1 to all set of our enzyme immunoassay of 11.

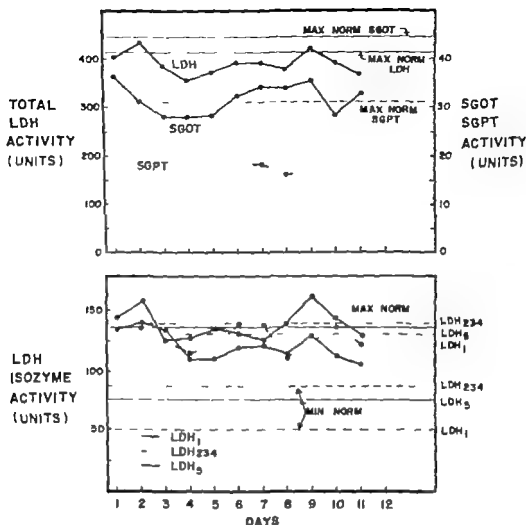


Fig. 2 The mean enzyme curves from 18 patients with acute coronary insufficiency are also plotted on the same scale as in Fig. 1.

remained elevated throughout the 11 days of study.

Coronary insufficiency. The daily number of subjects studied, mean enzyme values and number of abnormal enzyme values are reported in Table III. The mean enzyme curves are presented in Fig. 2. Five of the 18 subjects had no abnormality in serum enzyme activity.

The mean of the total LDH values for all patients with coronary insufficiency was above normal only on days 2 and 9. The mean result of LDH₁ was slightly increased throughout the period of study with peaks on days 2 (159 units) and 9 (163 units). A minimal elevation to 140 units of the mean LDH₂ and LDH₃

occurred on days 6 and 2 respectively.

Total LDH was minimally elevated (mean peak of 560 units) in 11 patients (61 per cent). Six of these 11 subjects had peak elevations before day 5 of these the predominant isoenzyme abnormality occurred in LDH₁ and LDH₂ in 3 cases in LDH₁ in 2 cases and equally in all isoenzyme fractions in 1 case. Total LDH in 3 of the 11 patients peaked after day 5 and the predominant isoenzyme abnormality occurred in LDH₁, LDH₂ plus LDH₃ and in all isoenzymes in 1 case each. In the other 2 patients early and late elevations of total LDH activity were present and associated with elevation of LDH₁ in one patient and with elevations

of LDH₁ (early peak) and LDH₂ (late peak) in the other.

The mean SGOT curve in the subjects with coronary insufficiency remained normal. SGOT was modestly elevated (mean peak of 60 units) in 8 subjects (44 per cent). The increases in SGOT occurred before day 5 in 3 of the 11 subjects; after day 5 in 3; and both early and late in the other 2 subjects. The 10 SGOT elevations observed in 11 patients were associated in 5 with increased LDH₂ and LDH₃ activity, in 4 with increased LDH₁ activity, and in 1 with normal isoenzyme activity.

Four of the late SGOT peaks described were associated with recurrent chest pain. The findings in 2 patients with associated SGOT and LDH isoenzyme abnormalities are illustrated in Figs. 3 and 4.

A modest abnormality in SGPT activity was observed in 3 cases (17 per cent) while the mean curve for SGPT remained normal. The observed elevations peaked before day 5 and accompanied SGOT elevations.

Significant or persistent abnormalities in liver function were not observed in these patients.

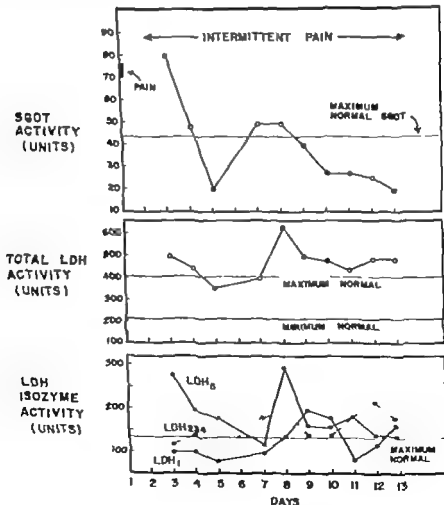


Fig. 3. The data enzyme activities are shown in a 33-year-old woman (E.S. No. 42346) with a typical picture of 1-month duration acute coronary insufficiency occurring 3 days before enzyme studies and intermittent chest pain occurring during the period of observation. This subject illustrates modest SGOT and total LDH elevations associated with elevated LDH₂ suggesting the presence of myocardial necrosis.

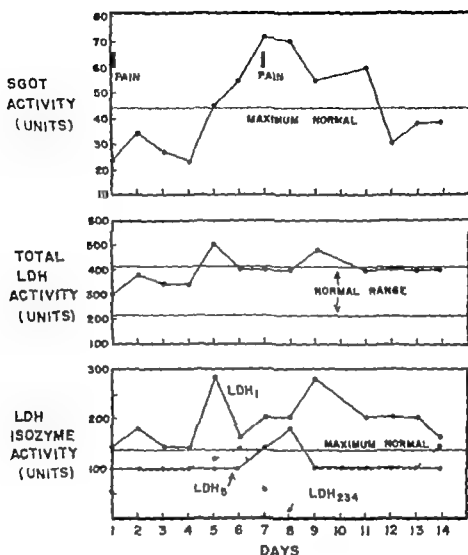


Fig 4 The enzyme curves from a 59 year-old man (H S No 233189) with a history of angina pectoris of 2 years duration acute coronary insufficiency occurring at onset of enzyme studies and recurrent coronary insufficiency on the seventh day of observation. The association of SGOT and total LDH elevations with abnormal LDH₁ activity is demonstrated in this case.

Discussion

Myocardial infarction. The serum activities of total LDH and SGOT may be increased in a variety of situations such as myocardial infarction, chronic congestive heart failure, hepatobiliary disease, muscular skeletal diseases, certain neoplasms and a number of hematological disorders. The isoenzymes of LDH have been helpful in differentiating myocardial infarction from many of the conditions noted above. Wroblewski and associates¹⁷ have described increased activity of LDH₁ and LDH₂ in transmural infarction. This in-

creased activity occurred earlier than that seen in SGOT and in total LDH, persisted for a number of days after SGOT and total LDH activity had returned to normal and was present in cases of subendocardial infarction in which SGOT and total LDH were normal. Several investigators^{11,12} have confirmed the abnormalities of LDH₁ in myocardial infarction and have commented upon the reliability of the LDH isoenzymes in distinguishing myocardial infarction from other cardiovascular diseases, hepatobiliary disease and the post-operative state.

The present study of uncomplicated myocardial infarction confirms the pattern of SGOT and total LDH activity described in previous investigations. The LDH₁ response in our cases was immediate significant (the mean was 5 times normal at maximum) and prolonged. The degree and duration of this response supports Wroblewski's concept that necrosis alone does not account for the enzyme activity observed.¹⁴ We have noted abnormalities of LDH₁ activity occurring both in the presence of normal total LDH and for a considerable time after total LDH has returned to normal.

Also of interest are the absolute elevations of LDH₁₁₄ and LDH₁ in these subjects. The activity of LDH₁₁₄ closely parallels that of LDH₁ and may well reflect the release of myocardial LDH₁. The increased LDH₁ however peaked on the fifth day and may reflect increased hepatic activity, since little LDH₁ is present in heart muscle. An increase in hepatic enzyme activity (aldolase, SGOT and LDH) has been described as a non-specific reaction to acute stress situations (exclusive of shock and cardiac or liver disease).¹⁵ The results of periodic hepatic function tests in our cases do not support acute hepatocellular dysfunction as a cause of increased LDH₁ activity although the more sensitive tests such as urine urobilinogen or BSP excretion were performed infrequently. In an earlier study from this clinic urobilinogen was found to be elevated frequently in patients with acute myocardial infarction.¹⁶

Coronary insufficiency. Experimental coronary insufficiency in the dog was not associated with increased SGOT activity unless myocardial necrosis occurred.¹⁷ A review of the SGOT test in angina pectoris and coronary insufficiency supports this concept.¹⁸ These reports and a subsequent review by Resnik¹⁹ describe patients with coronary insufficiency, non-specific changes in the electrocardiogram and abnormal SGOT activity implying the presence of infarction. A number of these cases reported in the literature have demonstrated either late or combined early and late elevation of SGOT activity similar to that seen in 5 of 18 cases in the present study. There is reason to believe

that some of these alterations in SGOT activity are hepatic and not myocardial in origin. We are not aware of previous studies of LDH isoenzyme activity or of consistent elevation of total LDH in coronary insufficiency.

The modest increases in total serum LDH observed in 11 of our 18 patients with coronary insufficiency occurred both early (less than 3 days) and late in relation to the onset of chest pain. The associated elevation of LDH₁₁₄ and LDH₁ in 6 of 11 subjects (both with early and late peaks) suggests myocardial necrosis. The elevation of LDH₁ activity in 6 of these same 11 patients and the borderline elevation of the mean LDH₁ for the group with coronary insufficiency as a whole may reflect increased hepatic enzyme release as discussed above. The 5 elevations of SGOT occurring early and late in association with the increases in LDH₁₁₄ and LDH₁ described above may also suggest infarction. It appears that SGOT, total LDH and LDH isoenzyme abnormalities are inconstant in acute coronary insufficiency and when present reflect myocardial necrosis in only approximately 50 per cent of cases if LDH₁ is a reliable index of necrosis.

Summary

In a prospective study, the serum activities of SGOT, SGPT, total LDH and the LDH isoenzymes 1, 2, 3, 4 combined and 5 were determined serially in 23 patients with acute myocardial infarction and 18 patients with acute coronary insufficiency.

In all of the 23 subjects with myocardial infarction there was a prompt marked and persistent elevation in serum activity of heart muscle lactic dehydrogenase (LDH₁) accompanied by a significant but less marked elevation of LDH₁₁₄ and LDH₁. Certain features of these changes are characterized and the associated SGOT and SGPT abnormalities are discussed.

The incidence and nature of the enzyme abnormalities occurring in 18 subjects with acute coronary insufficiency are discussed. If LDH₁ is a reliable criterion the isoenzyme results suggest that only 50 per cent of the observed elevations in

SCOT and total LDH activity are associated with myocardial necrosis.

Our study confirms the value of the serial analysis of LDH as a sensitive and more specific aid in the diagnosis of acute myocardial infarction. This test also will be of particular value in patients who present several days after clinical onset.

We would like to thank Mrs. Donald H. Lareau Jr. for her assistance in this study.

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Late systolic murmurs, clicks, and whoops arising from the mitral valve

A transeptal intracardiac phonocardiographic analysis

Donald F Leon MD

James J Leonard MD**

Frank W Kroetz MD***

William L Page MD

James A Sharer MD****

John F Lancaster MD*****
Pittsburgh Pa

The acoustical events which characterize the usual case of mitral insufficiency have been clearly defined. In most instances the murmur is high pitched pansystolic best heard at the apex and radiates toward the left axilla and left subscapular areas. Ventricular gallop rhythm, a short diastolic flow rumble and wide splitting of the second heart sound are observed in a significant number of cases of advanced mitral incompetence. The acoustical events associated with mitral stenosis are even better defined. These include accentuation of the first heart sound, the mitral opening snap and the characteristic long diastolic murmur.

In the past late systolic murmurs were thought to arise from the extracardiac areas.¹ The incidence of a history of pleural and pericardial disease was found to be high in patients with late systolic murmurs as well as in those who had systolic clicks or systolic gallops.^{2,3} The infrequently observed variety of musical murmur referred to as a systolic whoop by Levine and Harvey⁴ and Michaus⁵ in their respective texts has been attributed for the most part to epicardial sources and occasionally to intracardiac sources. This type of murmur has also been euphemistically referred to as a knock.

Recently a number of patients with late apical systolic murmurs have been demon-

** In the Department of Medicine, Division of Cardiology, University of Pittsburgh School of Medicine, Pittsburgh, Pa. This work was supported in part by Grant No. HE-08473-02 from the National Heart Institute, United States Public Health Service and was also supported in part by Grant No. H-13847 from the Health Research and Special Services Division, Pittsburgh, Pa.

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† Instructor in Medicine, Division of Cardiology, University of Pittsburgh School of Medicine, Pittsburgh, Pa. Present address: Research Fellow in Cardiology, St. James's Hospital, Dublin, Ireland.

‡ Assistant Professor of Medicine, Division of Cardiology, University of Pittsburgh School of Medicine, Pittsburgh, Pa. Present address: Professor of Medicine, Division of Cardiology, University of Pittsburgh School of Medicine, Pittsburgh, Pa.

§ Instructor in Medicine, Division of Cardiology, University of Pittsburgh School of Medicine, Pittsburgh, Pa. Present address: Professor of Medicine, Division of Cardiology, University of Pittsburgh School of Medicine, Pittsburgh, Pa.

¶ Present address: Research Fellow in Cardiology, St. James's Hospital, Dublin, Ireland.



Fig. 1 A No. 9F Ross transseptal catheter with a specially curved tip crossing the mitral valve and No. 5F phonocatheter passing through its lumen and extending 1 cm. beyond the tip of the Ross catheter. The pressure-conducting lumens can be seen between the phonocatheter and the Ross catheter.

in the regurgitant pathway above the mitral orifice. These patients may be distinguished from those who have pansystolic murmurs with late systolic accentuation in the left atrium but in whom only the late systolic vibrations are audible on the chest wall. The former group usually demonstrates only late systolic regurgitation by angiography whereas the latter group has pansystolic regurgitation. The former group tends to have small regurgitant volumes which is not necessarily the case in the latter group.

In each case of intracardiac late systolic murmur the sound pressure recording apparatus was withdrawn from the body of the left ventricle into the atrium the murmur was first recordable just below the mitral valve. At the level of the valve itself which was determined by atrialization of the ventricular pressure contour there was a distinct increase in intensity of the murmur. With further pullback into the body of the atrium the intensity of the murmur again diminished until it was not recordable near the septum or in

the atrial appendage. These observations would appear to define the precise origin of the murmur at the mitral orifice and lend further support to the already weighty evidence that this type of murmur is a regurgitant phenomenon.^{1,4}

Case 1 which is representative of the group of murmurs under consideration was that of a 61 year old woman without historical evidence of rheumatic fever but with a documented history of thyroid carcinoma with pulmonary metastases and malignant cells in the pleural fluid. She had been treated with radioactive iodine 3 years prior to study and there was no evidence of recurrence of the pulmonary lesions. At the time of cardiac investigation a carboangiogram revealed pericardial thickening.

The murmur recorded in the left atrium is the typical systolic murmur of late mitral insufficiency (Fig. 2). After the first heart sound there is a short period in which no murmur is seen. Thereafter a high pitched crescendo murmur with instances of fast activity peaks near the second sound and then rapidly terminates just after the sound of aortic valve closure. The continuance of the murmur beyond the aortic second sound is due to the time interval which occurs while the ventricular pressure is dropping from the aortic diastolic level to the level of left atrial pressure.

There is very little doubt that not too long ago this murmur would have been considered to be of extracardiac origin particularly in view of the history of pulmonary pleural and pericardial disease. Certainly the relationship between this type of murmur and pleuritis and pericarditis in the past is of more than circumstantial interest. There might well be a cause-and-effect relationship as yet undiscovered.

Case 2 is that of a 34 year old woman who had experienced repeated episodes of rheumatic fever and recent hyperthyroidism. Although she was asymptomatic a systolic murmur and click were present. Directly above the mitral valve there were a few soft murmur vibrations in early systole and a mid systolic click introducing a loud late systolic murmur. As the microphone was moved away from the valve the early systolic component

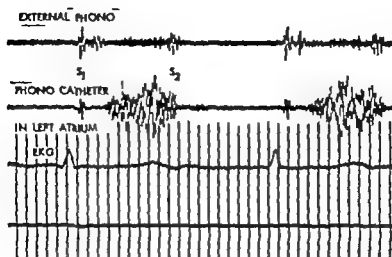


Fig. 2 The late systolic murmur of mitral insufficiency recorded in the left atrium in a patient with pericardial thickening and history of thyroid malignancy involving the lung and pleural space. A definite clear area is noted between the first sound (S₁) and the onset of the murmur in the left atrium. The murmur obscures the second sound (S₂). The second sound which follows S₁ on the external phonocardiogram is not recorded in the left atrium.

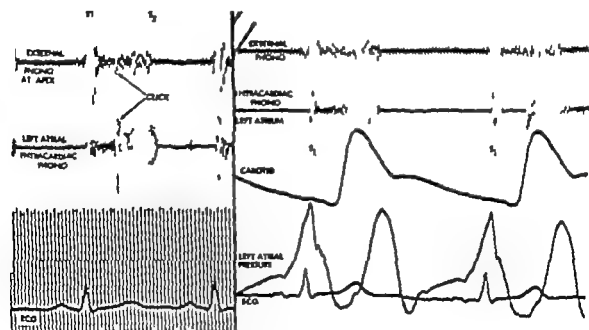


Fig. 3 A 48-year-old woman with a history of rheumatic fever and documented incompetence of the posterior mitral leaflet. The external apical phonocardiogram demonstrates a pansystolic murmur with late systolic accentuation. The late accentuation is interrupted by a click. The murmur includes the late accentuation. The late click is recorded in the mitral area by the intracardiac phonocatheter (left panel). In the right panel two complexes are seen. The first is recorded closer to the mitral valve and the second is further back from the valve. As the microphone is withdrawn from the mitral orifice the early components of the murmur disappear completely, whereas the click and late systolic murmur are preserved. The aortic and radial of the left atrial pressure pulse are clearly identified.

of the murmur disappeared (Fig 3) This phenomenon has been repeatedly observed in the past⁹

The time interval between the first sound and the click which introduces the murmur varied from beat to beat Selective left ventricular cineangiocardiographic study revealed regurgitation limited to the posterior mitral leaflet It was not possible to determine whether the incompetent leaflet was prolapsed However the intra atrial phonocardiogram displays the type of murmur and click reported in cases of prolapse of the leaflets⁷

Case 3 is that of a 26 year old woman who had experienced rheumatic fever as a child She was asymptomatic when a murmur was recently detected Phonocardiographic recordings demonstrated a late systolic regurgitant murmur introduced by a click Transseptal phonocardiograms showed this click and murmur to be arising from the mitral orifice The cineangiogram revealed minimal mitral regurgitation and all other hemodynamic data were normal

Case 4 is that of a 39 year old man who was known to have a heart murmur at the age of 16 years and whose first electrocardiogram at that time revealed right bundle branch block There was no history of rheumatic fever and the patient's exercise tolerance had remained normal Fig 4 shows the late systolic murmur recorded in the left atrium in association with right bundle branch block Mild mitral regurgitation was documented by biplane angiocardiography

Right bundle branch block is shown delaying the sound of pulmonary valve closure and the sound of aortic valve closure is in the terminal vibrations of the murmur Thus the murmur of late mitral insufficiency in the presence of delayed pulmonary valve closure might at first be mistaken for an ejection murmur

This murmur when recorded above the mitral orifice has many late vibrations of such high frequency that they exceed the limits of the recorder in the same fashion as do the vibrations of the phenomenon known as systolic whoop (see Fig 7)

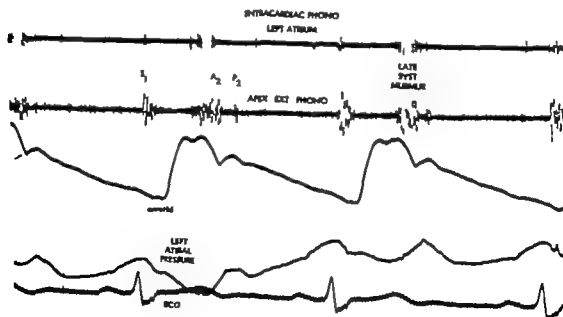


Fig. 4 The late systolic murmur of mitral regurgitation recorded in the left atrium of 39 year old man. The delay of pulmonary valve closure (P) related to right bundle branch block (ECG) is 1 Int a the normal left atrial pressure (a and b) The regurgitant murmur extends up to aortic valve closure (c) identified by the maxima of the radial carotid pulse

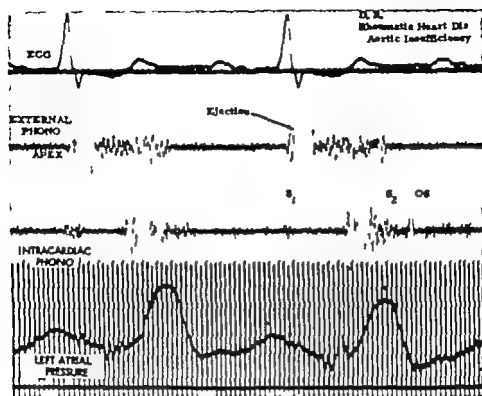


Fig. 5. A 54-year-old man with the late systolic murmur of mild mitral insufficiency related to left ventricular hypertrophy and dilation and dominance of the anterior cusp. The earlier ejection murmur can be seen to blend with the late systolic murmur to occupy all of systole in the external phonocardiogram. The late systolic regurgitant murmur and an opening snap (OS) in the absence of mitral stenosis are recorded in the left atrium.

Case 1 is that of a 54-year-old man with clear clinical and angiographic evidence of rheumatic aortic insufficiency. A mitral regurgitant systolic murmur was easily heard at the apex by every observer and it was thought by all except one to be pingsystolic. This single observer maintained that the early vibrations heard at the bedside were referred to the apex from the aortic ejection murmur and that the typical murmur was limited to the latter part of systole. Simultaneous left atrial sound pressure recordings definitely established the presence of late systolic regurgitation with normal atrial pressure where is the external phonocardiogram recorded the additional early ejection murmur (Fig. 5). A mitral opening snap was repeatedly recorded near the mitral valve in this patient in whom there was no mitral stenosis. Selective left ventricular cine angiography demonstrated minimal regurgitant opacification of the left atrium.

At the time of operation for aortic insufficiency a mitral regurgitant jet could not be felt when the left atrium was invaginated. The mitral valve was not visually inspected at operation. The patient died postoperatively and autopsy revealed a jet lesion on the posterior wall of the left atrium thus indicating that some mitral regurgitation had been present. The posterior mitral leaflet was of normal thickness and both sets of chordae tendineae were normal. The anterior mitral leaflet was considerably larger than the posterior leaflet. It had become slightly thickened by the aortic regurgitant jet. Closure was accomplished by the dominant anterior leaflet covering some of the area usually covered by posterior leaflet substance. The left ventricle including the papillary muscles was dilated and hypertrophied. The mechanism of mitral regurgitation appeared to be that the dilated and hypertrophied left ventricle

coupled with the hypertrophied papillary muscles held the small posterior leaflet deeper in the ventricular cavity than usual during systolic contraction thus permitting the larger anterior leaflet to slip by the edge of the posterior leaflet as ventricular volume decreased during late ventricular ejection. Thus late systolic mitral insufficiency was found to be related to ventricular hypertrophy and cusp dominance in the absence of rheumatic distortion of the mitral valve.

Case 6 is that of a 44 year old woman with surgically documented rheumatic mitral valve disease. She previously had undergone two mitral commissurotomy and was suffering again from a recurrence of symptoms. Clinical evaluation and catheterization indicated the presence of predominant mitral stenosis with some mitral insufficiency and pulmonary hypertension. A systolic regurgitant murmur

occurring early in systole and ending with a mid systolic click was audible and recordable externally. The intracardiac microphone (Fig 6) recorded the click in the left atrium in the region of the mitral valve. The patient underwent surgical excision of the mitral valve and its supporting structure and a mitral prosthetic valve was installed. Postoperatively the click was no longer present. Thus in a patient with two previous episodes of pleuritis and pericarditis each surgically induced the systolic click appears to have originated at the mitral valve rather than arising from the pericardial surface.

Furthermore this case might well complete the spectrum of timing of mitral regurgitant murmurs in that the murmur was limited to early systole and was terminated by a click. This circumstance may be explained by a surgically induced valvular deformity in which regurgitation would

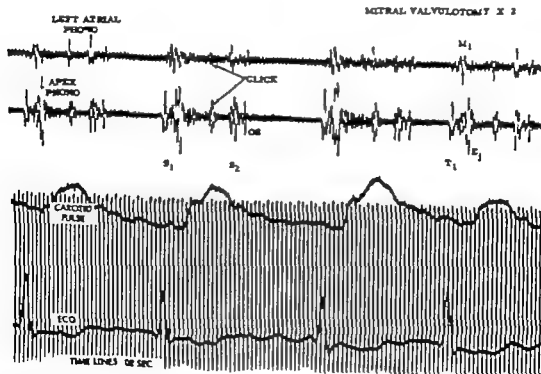


Fig. 6. A 44 year old woman with recurrent mitral stenosis in whom a systolic click was identified in the apex phonocardiogram. The intracardiac microphone would record this click only near the mitral orifice. The click can be seen in terminate an early regurgitant murmur. Tricuspid (T) and mitral (M) components of the first sound and a pulmonary ejection sound (E_1) are identified as well as the second sound (S) and opening snap (OS).

abnormal attachment of chordae tendineae or dysfunction of a papillary muscle related or not to myocardial infarction.¹² Several patients with systolic whoops have had arteriosclerotic heart disease⁴ and 1 patient known to the authors but not reported in this study had laboratory and autopsy evidence of mitral insufficiency, previous myocardial infarction and an abnormal papillary muscle.

Case 8 is that of a 55 year-old man with a 7 year history of progressive cardiomegaly of obscure etiology. There were no signs or symptoms of coronary artery occlusive disease but severe congestive failure had been present for 1 year prior to investigation. A moderately high pitched systolic whoop was audible at the bedside. The whoop was present on full inspiration and usually absent on expiration. It was also prominent in the first few beats after an extrasystole. Its duration, timing and intensity varied from time to time although it was never heard in diastole or

during the period of ventricular isovolumetric contraction. A Grade 1 presystolic murmur of mitral insufficiency was also audible. The systolic whoop recorded above the mitral orifice (Fig 8) was of greater intensity than when recorded below the mitral valve or elsewhere within the left heart or externally. It was not heard in the right heart. The whoop had its onset after isovolumetric systole and was of variable duration. The pansystolic regurgitant murmur had the same distribution as the whoop. During the recording of Fig. 8 there were no catheters traversing the mitral valve thus excluding the phenomenon noted in the previous case.

Because of its respiratory and positional variation this whoop previously would have been considered to arise from an extracardiac mechanism. However the regurgitant nature of this whoop is clearly revealed by the left heart sound pressure recordings. Cineangiocardiograms documented the presence of slight mitral in-

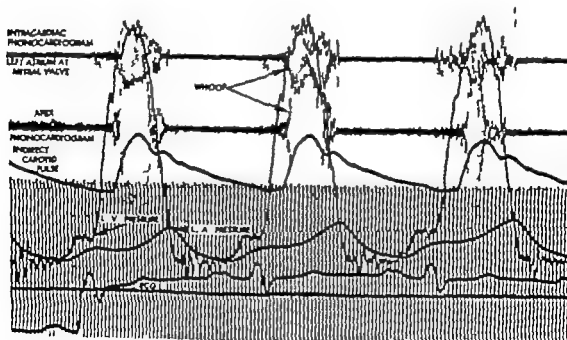


Fig 1 A 55 year-old man with primary myocardial infarction and mitral insufficiency and an intermittent systolic whoop recorded best above the mitral valve. The whoop has the intracardiac distribution and timing of a normal regurgitant murmur. Its presence varies with respiration, body position and the presence of extracardiac extrasystoles. Its intensity and duration varies from beat to beat. The murmur extends through L and masks the sounds of valve closure. Left: intracardiac pressure was obtained through retrograde aortic catheter.

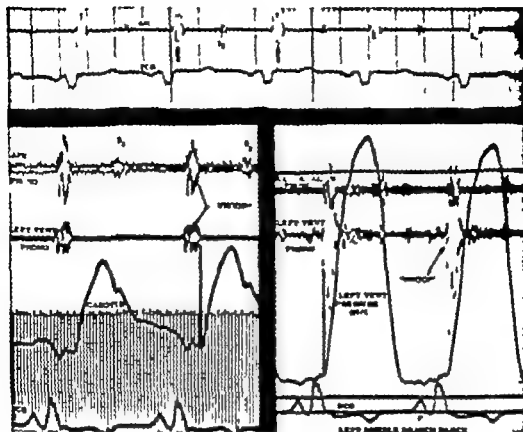


Fig. 9. A 37-year-old man with a normal sinus rhythm and left bundle branch block (LBBB). The whoop sound during the systolic contraction is identified in the apical phonogram (upper right). With an intra-aortic catheter, the whoop was located to the left ventricular inflow tract (left lower right) with the first sound of the aortic valve closure (left lower left) and the whoop sound (left lower right) identified as the first sound of the aortic valve closure (left lower right) that limiting the whoop to the monovolumetric contraction (upper right).

competence and what appeared to be adequate coronary vessels.

Case 9 is that of a 37-year-old woman who was hospitalized because of acute bronchitis. There was no previous history of rheumatic fever or pericarditis and the patient had no cardiovascular symptoms. Left bundle branch block was found on a routine electrocardiogram. An early systolic whoop beginning with the first sound was recorded externally and with the intra-aortic microphone. This whoop was localized to the left ventricular inflow tract in the region of the mitral chordae (Fig. 9). This whoop occurred during the period of monovolumetric contraction. At this time, the papillary muscles are putting the chordae tendineae on the stretch to fix the mitral valve in the closed position. All left heart pressures were normal and

there was no evidence of mitral insufficiency or stenosis.

Discussion

The evaluation and interpretation of murmurs and other acoustic events recorded within the left atrium should not be approached casually. It is important to realize that in some instances the same mitral regurgitant murmur has different durations and configurations when recorded in various areas of the atrium. This is best explained in the cineangiographic demonstration of the mitral regurgitant jet being played across the atrium in much the same fashion a one applies paint with a paint spray. Thus it is possible in any particular part of the atrium to sample only a portion of a murmur. It is obvious then that the only area

in which mitral regurgitant acoustical events may be recorded with certainty is the area of the mitral orifice. A good technique for assuring adequate sampling of the mitral orifice is to withdraw the recording device from the body of the left ventricle into the left atrium during recording.

As a result of study of these 9 patients with transeptal sound and pressure methods simultaneously the late systolic murmur has been shown to be a mitral regurgitant murmur in the 5 cases in which it was present. In addition the mitral origin of three systolic clicks has been clearly demonstrated: one introducing late systolic mitral regurgitation, another probably related to a bulging posterior leaflet and a third terminating an early systolic regurgitant murmur. Two instances of systolic whoop have been shown to be mitral regurgitant phenomena and an early systolic whoop occurring during isovolumetric contraction has been localized to the region of the chordae tendineae. One of the regurgitant whoops was limited to late systole whereas the other varied in duration. The precise localizing nature of the technique employed has proved that all of these acoustical events arise directly from the mitral valve and its supporting structures.

It has long been appreciated that the usual clue of mitral insufficiency regardless of etiology may be recognized by the presence of a typical pansystolic regurgitant murmur. For many years late systolic murmurs, systolic clicks and whoops were thought to arise from extracardiac mechanisms and for the most part not to reflect significant mitral pathology. The evidence supporting these impressions was mostly circumstantial. It has certainly been thought by most observers that a large number of patients with these physical findings had histories of pleural and pericardial disease but the pericardial disease was often rheumatic.

Recently it has been shown that some late systolic murmurs whether introduced by a click or not are associated with mild mitral regurgitation. In addition it is now apparent that systolic whoops reflect mitral insufficiency in some cases and that late systolic murmurs, clicks and whoops make up the auscultatory continuum of mild mitral insufficiency.

The high incidence of pericardial disease in patients with late systolic murmurs and systolic clicks should not be dismissed lightly. Perhaps in some cases pericardial inflammation and thickening might distort the supporting structures of the mitral valve or its annulus or alter the contraction characteristics of papillary muscle as is suggested by the fact that in Case 1 there was certain evidence of late systolic mitral insufficiency in a patient with a history of pleural and pulmonary metastases and documented pericardial thickening at the time of cardiac investigation.

Even so it would not be reasonable to infer that every instance of systolic click and whoop represents mitral insufficiency. These events can and do arise from other cardiac valves and perhaps by other mechanisms.

Summary

Nine patients were studied by means of a modification of the Ross transeptal catheterization technique which permits simultaneous recording of sound and pressure in the left heart chambers. In the 5 patients with late systolic murmurs these murmurs were shown to arise in the mitral area and to radiate into the left atrium thus documenting their regurgitant nature. One of these patients had a thickened pericardium. Three instances of systolic clicks were localized to the mitral valve: one with late mitral insufficiency probably due to a prolapsed leaflet, one introducing a late regurgitant murmur and the third terminating an early regurgitant murmur. A late systolic whoop artificially induced was found to be regurgitant in character and a late systolic whoop of varying duration naturally occurring was also found to be regurgitant. An early systolic whoop occurring during isovolumetric contraction was localized to the subvalvular supporting structure. It has become apparent from the study of these cases that late systolic murmurs, systolic clicks and systolic whoops constitute a continuum of acoustical events which are associated with mitral insufficiency.

Some speculation has been made concerning the possible relationship of pericardial disease and these mitral acoustical events.

Addendum

Since the preparation of this manuscript a case of late systolic murmur introduced by a click has been shown by Perloff, Roman and Harvey¹⁴ to emanate from the mitral valve.

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Table I Part I

Parameter	Cardiac index (L/min/M ²)	Stroke volume index (cc/M ²)	Mean palm art pressure (mm Hg)	Mean brachial art pressure (mm Hg)	Rt minute work index (kg M/M ²)
Control	3.75 (2.7-4.9)	49.5 (34-56)	12.8 (8.5-18)	91.0 (80-111)	0.66 (0.44-0.99)
Test	11.24 (4.4-17.8)	54.3 (43-72)	15.1 (11-19)	59.0 (43-80)	1.30 (0.74-1.86)
Per cent change	+66	+10	+18	-35	+95
p value	<0.001	<0.02	<0.001	<0.001	<0.001

Table II Part II

Parameter	Pulmonary arterial systolic pressure (mm Hg)	Pulmonary arterial diastolic pressure (mm Hg)	Rt systolic pressure (mm Hg)	Rt diastolic pressure (mm Hg)	Brachial arterial systolic pressure (mm Hg)	Brachial arterial diastolic pressure (mm Hg)
Control	19 (13-26)	8.2 (4-17)	25 (15-35)	4.3 (2-9)	116 (100-148)	72 (54-90)
Test	33 (17-32)	8.7 (4-19)	27 (19-37)	7.7 (1-14)	84 (58-104)	47 (36-58)
Per cent change	+22	+7	+8	-38	-27.6	-34.5
p value	<0.001	0.5	<0.01	<0.05	0.001	0.001

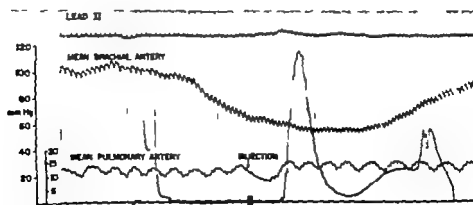


Fig. 1 Simultaneous ly recorded mean brachial and pulmonary arterial pressures with a quantitative indicator dilution curve described after inhalation of amyl nitrite. There is a rise in the mean pulmonary arterial tracing at the time of maximal decline in systemic arterial pressure. See text for details.

RV stroke work index (Gm M/V)	LV stroke work index (M/V)	LV stroke work index (Gm M/V)	Pulmonary vascular resistance (dynes sec cm ⁻⁵)	Systemic vascular resistance (dynes sec cm ⁻⁵)	Heart rate (per min)	Rectitude time (sec)
8.8 (3.6-13.7)	4.40 (2.8-6.0)	56.2 (25.6-87)	146 (85-309)	943 (651-1478)	77 (60-90)	11.7 (14-18)
11.7 (8.0-16.4)	4.68 (2.76-6.65)	40.8 (31-58.5)	95 (60-176)	414 (270-822)	115 (96-138)	8.4 (7-10)
+27	+7	-27	-33	-56	+30	-28
<0.01	0.5	<0.01	<0.01	<0.001	<0.001	<0.001



Fig. 2. At the onset of the decline in brachial arterial pressure there is a rise in mean pulmonary arterial pressure which is maintained for the duration of the decline in systemic pressure. See text for details.

observations were then made after the inhalation of amyl nitrite (Figs 1 and 2). The following data were derived (Table I): cardiac index, stroke index, mean pulmonary arterial and brachial arterial pressures, right ventricular and left ventricular minute and stroke work indices, total pulmonary and systemic vascular resistance, heart rate, and mean rectitude time of injected indicator.

Part II. Thirty minutes after the initial inhalation of amyl nitrite, sequential control tracings were taken of the undamped pulmonary arterial and right ventricular pressures while simultaneously recording the undamped brachial arterial pressure and the electrocardiogram. The catheter was readvanced into the pulmonary artery, and similar observations were made at the

height of the amyl nitrite effect. The systolic and diastolic pressures in the pulmonary artery, right ventricle and brachial artery were then measured (Table II).

Part III. Twenty to 30 minutes after completion of Part II, the following observations were made on 3 subjects. Calibrated amounts of indocyanine green dye were injected into a large median basilic vein via a No. PE 50 polyethylene catheter, and dilution curves were inscribed by withdrawal from the pulmonary artery via the intracardiac catheter. Similar tracings were recorded at the height of the amyl nitrite effect (Fig. 3). It is recognized that the use of a cardiac catheter as the afferent limb of the withdrawal system may introduce inaccuracies in the absolute values of flow determina-

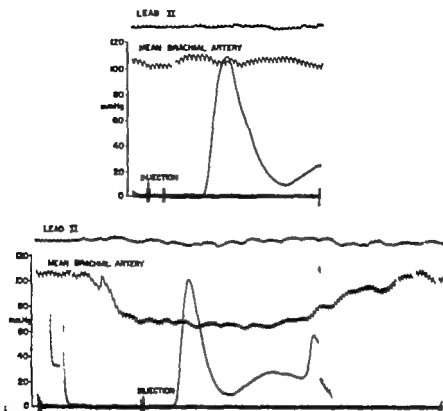


Fig 3 Upper: Mean brachial arterial pressure and a control dilution curve obtained by withdrawing from the pulmonary artery in the atherer after injection of Cardiogreen to a medium in the cm. Lower: The same tracings after the inhalation of amyl nitrite. The area under the dilution curve has diminished reflecting an increase in flow.

tions.⁸ However, the method was not employed for the calculation of absolute values. The dilution curves were used only for comparative quantification in order to estimate directional changes in pulmonary blood flow with each patient serving as his own control.

Results

Part I (Table I)

CARDIAC OUTPUT The average control cardiac index was 3.75 L/min/M^2 with a range of 2.7 to 4.9. At the height of the amyl nitrite effect the average was 6.24 L/min/M^2 with a range of 4.47 to 7.8, representing a significant increase of 66 per cent ($p < 0.001$).

STROKE VOLUME The average control stroke volume index was 49.5 ml/M^2 with a range of 34 to 56. At the height of the amyl nitrite effect the average was 54.3 ml/M^2 with a range of 43 to 72

representing a slight increase of 10 per cent ($p < 0.02$).

MEAN PULMONARY ARTERIAL PRESSURE The average control mean pulmonary arterial pressure was 12.9 mm Hg with a range of 9.5 to 15. At the height of the amyl nitrite effect the average was 15.1 mm Hg with a range of 11 to 19, representing a small but significant increase of 18 per cent ($p < 0.001$).

In 4 instances there was a rise of 2 to 4 mm Hg in mean pulmonary arterial pressure at the onset of the fall in brachial arterial pressure.

MEAN BRACHIAL ARTERIAL PRESSURE The average control brachial arterial mean pressure was 91 mm Hg with a range of 80 to 111. At the height of the amyl nitrite effect the average was 59 mm Hg with a range of 43 to 80, representing a significant decline of 35 per cent ($p < 0.001$).

RIGHT VENTRICULAR MINUTE WORK The

average control effective right ventricular minute work index was 0.66 kg M/M with a range of 0.44 to 0.99 . At the height of the amyl nitrite effect the average was 1.30 kg M/M^2 with a range of 0.74 to 1.86 representing a significant increase of 95 per cent ($p < 0.001$).

LEFT VENTRICULAR MINUTE WORK. The average control effective left ventricular minute work index was 4.40 kg M/M with a range of 2.8 to 6.0 . At the height of the amyl nitrite effect the average was 4.68 kg M/M with a range of 2.76 to 6.65 representing an insignificant change of 7 per cent ($p < 0.5$).

RIGHT VENTRICULAR STROKE WORK. The average control effective right ventricular stroke index was 8.9 Gm M/M with a range of 5.6 to 13.7 . At the height of the amyl nitrite effect the average was 11.2 Gm M/M with a range of 8.0 to 16.4 representing a significant increase of 27 per cent ($p < 0.01$).

LEFT VENTRICULAR STROKE WORK. The average control effective left ventricular stroke work index was 56.2 Cm M/M^2 with a range of 27.6 to 82 . At the height of the amyl nitrite effect the average was 40.6 Cm M/M^2 with a range of 31 to 58 representing a significant decline of 27 per cent ($p < 0.01$).

PULMONARY VASCULAR RESISTANCE. The average control total pulmonary vascular resistance was $146 \text{ dynes sec cm}^5$ with a range of 85 to 309 . At the height of the amyl nitrite effect the average was $98 \text{ dynes sec cm}^5$ with a range of 60 to 176 representing a significant decline of 33 per cent ($p < 0.01$).

SYSTEMIC VASCULAR RESISTANCE. The average control systemic vascular resistance was $944 \text{ dynes sec cm}^5$ with a range of 674 to 1475 . At the height of the amyl nitrite effect the average was $414 \text{ dynes sec cm}^5$ with a range of 270 to 522 representing a significant decline of 56 per cent ($p < 0.001$).

HEART RATE. The average control heart rate was 77 beats per minute with a range of 60 to 90 . At the height of the amyl nitrite effect the average was 115 per minute with a range of 96 to 134 representing a significant increase of 50 per cent ($p < 0.001$).

CIRCULATION TIME. The average control

recirculation time was 11.7 seconds with a range of 14 to 18 . At the height of the amyl nitrite effect the average was 8.4 seconds with a range of 7 to 10 representing a significant decline of 28 per cent ($p < 0.001$).

Part II (Table II)

PULMONARY ARTERIAL SYSTOLIC PRESSURE. The average control pulmonary arterial systolic pressure was 19 mm Hg with a range of 13 to 26 . At the height of the amyl nitrite effect the average was 23 mm Hg with a range of 17 to 32 representing a significant increase of 22 per cent ($p < 0.001$).

PULMONARY ARTERIAL DIASTOLIC PRESSURE. The average control pulmonary arterial diastolic pressure was 8.2 mm Hg with a range of 4 to 17 . At the height of the amyl nitrite effect the average was 8.7 mm Hg with a range of 4 to 19 representing an insignificant increase of 7 per cent ($p < 0.5$).

RIGHT VENTRICULAR SYSTOLIC PRESSURE. The average control right ventricular systolic pressure was 25 mm Hg with a range of 15 to 35 . At the height of the amyl nitrite effect the average was 27 mm Hg with a range of 19 to 37 representing a small but significant increase of 8 per cent ($p < 0.01$).

RIGHT VENTRICULAR DIASTOLIC PRESSURE. The average control right ventricular diastolic pressure was 4.3 mm Hg with a range of 2 to 9 . At the height of the amyl nitrite effect the average was 2.7 mm Hg with a range of 1 to 4 representing a decline of 39 per cent ($p < 0.05$).

BRACHIAL ARTERIAL SYSTOLIC PRESSURE. The average control brachial arterial systolic pressure was 116 mm Hg with a range of 100 to 148 . At the height of the amyl nitrite effect the average was 84 mm Hg with a range of 58 to 104 representing a significant decline of 27.6 per cent ($p < 0.001$).

BRACHIAL ARTERIAL DIASTOLIC PRESSURE. The average control brachial arterial diastolic pressure was 77 mm Hg with a range of 54 to 90 . At the height of the amyl nitrite effect the average was 47 mm Hg with a range of 36 to 59 representing a significant decline of 34 per cent ($p < 0.001$).

Part III

QUANTIFICATION OF INDICATOR DILUTION CURVES OBTAINED BY PERIPHERAL VENOUS INJECTION WITH PULMONARY ARTERIAL WITHDRAWAL (Fig 3) The average control quantification was 2.97 L/min/M^2 . At the height of the amyl nitrite effect the average was 5.38 L/min/M^2 .

Discussion

Amyl nitrite by interfering with the enzymatic decomposition of adenosine triphosphate deprives arterial smooth muscle of the energy required for the maintenance of tone thus initiating vasodilation.¹⁰ The systemic hemodynamic effects of this pharmacologic intervention include: (1) a decrease in arterial pressure, vascular resistance, stroke work, circulation time, level of the dirotic notch, amplitude of the dirotic wave and duration of the diastolic filling period; (2) an increase in heart rate, cardiac index and ejection velocity; and (3) no change in stroke volume or minute work. During the course of the present study, many of these systemic circulatory parameters were of necessity reinvestigated and the findings were in close agreement with prior observations.⁶

Effects on pressure and flow in the pulmonary circulation. Amyl nitrite causes a marked, consistent increase in systemic flow per minute.¹¹ Whether the drug exerts a similar effect on pulmonary blood flow has been unsettled. In the dog, nitroglycerin increases left ventricular output more than it increases venous return to the right heart; the difference being derived from the thoracic reservoir.¹² However, this reservoir appears to be insufficient to permit increases in systemic output of the degree induced by amyl nitrite unless a compensatory increase in venous return occurs.¹³ This thesis is supported by the uniform rise in right ventricular systolic pressure after the inhalation of amyl nitrite by patients with pulmonary stenosis¹⁴ and is in accord with the small but significant increases in both systolic and mean pulmonary arterial pressures after the administration of amyl nitrite in this study (Fig 2, Tables I and II). Estimates of nitrite-induced directional changes in pulmonary blood flow in 3 subjects so studied (Fig 3) suggested that venous

return increased roughly in parallel with the augmentation of systemic output. Should an increase in venous return be of the same order as the increment in cardiac output, then the pulmonary vascular resistance would of necessity decline (Table I). However, the magnitude of this decline is far less than the fall in systemic resistance (Table I).¹⁵ These data do not indicate whether the lesser circulation dilates passively to accommodate the increase in flow or whether amyl nitrite exerts a direct vasodilatory effect. The drug does appear to act as an active dilator in the vasoconstrictive pulmonary hypertension of large ventricular septal defect in which the left to right shunt provides a pathway for the entry of relatively undiluted nitrite into the pulmonary circulation.¹⁶ Response to the drug in this context may therefore relate to the increased concentration of active principle acting upon highly vasoactive arterioles.¹⁷ In the presence of a normal circulation, relatively dilute nitrite enters a less reactive pulmonary bed. Although the drug may still exert a direct effect in normal man, additional passive dilatation remains a plausible consideration with regard to the primary pharmacologic influence on the pulmonary vascular resistance.⁶

The small but significant nitrite-induced rise in pulmonary systolic pressure with little or no change in diastolic pressure resulted in a modest increase in pulse pressure (Table II). The contour of the pulmonary arterial pulse including the level of the dirotic notch remained unchanged after the inhalation of amyl nitrite in contrast to the marked alterations in systemic arterial contour.⁶ There was a slight but significant increase in right ventricular systolic pressure with a 38 per cent decline in diastolic filling pressure (borderline significance) (Table II).

Opinion differs with regard to the effect of amyl nitrite upon the systemic venous bed; some authors hold that the drug induces venoconstriction¹⁸ whereas others believe that venodilatation occurs.¹⁹ In dogs on right heart bypass with fixed systemic outputs,²⁰ amyl nitrite induces an initial transient increase in venous return as the systemic arterial pressure begins

to fall but subsequently induces a decrease in venous return as the systemic pressure falls maximally. These observations suggest that the initial effect is reflex venoconstriction in response to the fall in systemic arterial pressure and that the subsequent effect is venodilatation in response to the direct effect of the drug upon the venous bed. In the light of this information it was pertinent that 4 of our subjects showed a small distinct rise in mean pulmonary arterial pressure at the onset of the fall in brachial arterial pressure (Fig. 2). This suggests that in man the inhalation of amyl nitrite may induce an initial increase in venous return due to transient venoconstriction followed by an additional increase in venous return associated with augmented cardiac output.

Effect on ventricular work (Table I)
Since amyl nitrite caused only a moderate decline in pulmonary resistance the mean pulmonary arterial pressure rose slightly in the face of the large increment in flow. Accordingly, right ventricular minute work increased appreciably. Furthermore the rise in pulmonary mean pressure occurred with a relatively constant stroke volume so that right ventricular stroke work rose although to a lesser degree than work per minute.

These results were in marked contrast to the effect of amyl nitrite on left ventricular work.² The increase in cardiac output was uniformly associated with a fall in systemic arterial pressure that was sufficient to leave left ventricular minute work relatively constant. Since stroke volume changed little if at all as systemic pressure fell left ventricular stroke work regularly and strikingly decreased. Thus amyl nitrite had opposite effects upon the two ventricles and appeared to be a pharmacologic means of selectively stressing the right heart.

Diagnostic implications of the foregoing effects of amyl nitrite Under the influence of amyl nitrite the gradient and murmur of tricuspid stenosis increase because of augmented flow into the right atrium together with a shortened diastolic filling period.¹⁴ As the right ventricle is stressed tricuspid regurgitant flow should increase and the murmur of tricuspid incompetence should get louder.¹⁵ In pul-

monary stenosis with intact ventricular septum² the increase in circulatory flow rate and venous return augment both the gradient and the murmur. In patients with mild pulmonary stenosis and nondynamic gradients, the inhalation of amyl nitrite may induce a significant difference in right ventricular-pulmonary arterial systolic pressures in a fashion analogous to the effect of the drug in occult obstruction to left ventricular outflow.⁶ In cyanosed Fallot's tetralogy¹⁶ the ventricular septal defect permits the right ventricular pressure to fall in parallel with the decline in systemic pressure so that the right-to-left shunt increases the pulmonary flow diminishes and the murmur becomes shorter and softer. Maintenance of pulmonary arterial diastolic pressure in nonvasoreactive pulmonary hypertension should prevent a decrease in the Graham Steell murmur whereas a uniform fall in systemic diastolic pressure regularly reduces the intensity of the murmur of aortic incompetence. The disproportionate fall in systemic vascular resistance diminishes left-to-right shunts through nonpulmonary hypertension and aortopulmonary or interventricular communications. On the other hand in the presence of patent ductus with fixed pulmonary hypertension and a balanced shunt the inhalation of amyl nitrite may cause diagnostic differential cyanosis by selectively decreasing systemic arterial pressure.

Summary

Amyl nitrite has assumed a role of considerable importance in clinical auscultation of the heart and in the phonocardiographic and physiologic evaluation of the cardiac patient. The systemic hemodynamic effects of the inhalation of amyl nitrite were recently investigated in this laboratory. The purpose of the present study was to extend these observations to the lesser circulation.

Results indicate that the inhalation of amyl nitrite in normal man causes (1) a marked increase in blood flow which is primarily rate related, (2) a profound decline in total systemic resistance resulting in a decline in left ventricular stroke work but no change in left ventricular minute work, (3) a less profound decline in total

pulmonary resistance (4) a small but significant rise in pulmonary arterial systolic and mean pressures and (5) an increase in effective right ventricular minute and stroke work. Diagnostic implications were briefly discussed. Knowledge of the circulatory action of the drug in normal man should enhance its usefulness in disease states.

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Optical behavior of indocyanine green dye in blood and in aqueous solution

William F. Sutler III S*

Schuyler E Hardin

Robert H. Benson

L Jerome Kervets M D Ph D

Gerald L. Schreiber M.D.

Gentle Flo

One major advantage of the use of indocyanine green dye for indicator dilution curves is the occurrence of its minimum light absorption at a wave length of 800 millimicrons in plasma. This dye thus facilitates recording of indicator dilution curves independent of variations in oxygen saturation.³

The use of the dye dilution technique for the determination of cardiac output and/or the magnitude of shunts necessitates calibration of the sensitivity of the densitometer to known concentrations of blood dye mixtures. It follows that the densitometer must be stable and capable of giving an identical output for any given concentration of dye in whole blood. Techniques and instruments have been developed which are capable of recording calibration curves to this high degree of accuracy. These techniques and instrumentation have been used successfully for a number of years. Recently, however, at the University of Florida Techni-

Hospital there was a period of time during which it was virtually impossible to obtain stable and reproducible dye dilution calibration curves with the use of Cardio Green dye in heparinized fresh whole blood. Extensive checks of the densitometers determined that they were operating satisfactorily. It was found that fresh blood heparinized with an anticoagulant known as Lipo Heparin[†] which contains a small amount of sodium bisulfite used as a preservative caused a significant and apparently erratic decrease in light absorption and vitiated the calibration. Correspondence with other laboratories showed that they had had similar experiences.

Therefore the purpose of this paper is to draw attention to the behavior of indocyanine green dye in the presence of sodium bisulfite and in aqueous solutions. Empirical data and a discussion are offered for consideration; it is those using these dye detection techniques. Although the optical

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behavior of indocyanine green dye discussed in this communication is well known to dye chemists it has been often overlooked by people using this dye for diagnostic and investigative procedures.

Effect of Lipo Heparin and Liqueamin Sodium 10 on static calibration of the densitometer. Blood was withdrawn from normal subjects and half of it was heparinized with Liqueamin Sodium 10* and half with Lipo Heparin. Both of these anti-coagulants are rendered isotonic by the addition of sodium chloride and sodium hydroxide is added to adjust the pH of Lipo Heparin to a mean value of 7 with a range of 6.8 to 7.2* where as the pH of Liqueamin Sodium 10 is adjusted to a mean value of approximately 6.8 with a range of 6.5 to 7.5*. Two sets of dye dilutions were made each set consisting of three concentrations of dye at 0.6 and 12 mg per liter. These samples were then drawn through a densitometer by a constant withdrawal syringe set at 191 cc per minute† and the output of the densitometer was recorded on an 1108 Honeywell Recorder. The resulting calibration curves are shown in Fig. 1. Notice the marked difference in the recorded deflections of the galvanometer for identical concentrations of dye.

Loss of light absorption of approximately equal magnitude was demonstrated repeatedly with the use of fresh whole blood anticoagulated with Lipo Heparin. Moreover a similar phenomenon has been observed approximately thirty times in diagnostic procedures when Lipo Heparin was used. Absorption of light at 800 mμ was also found to be extremely unstable with respect to time. Dye blood solutions anticoagulated with Lipo Heparin often changed with time from that shown in Fig. 1 to a calibration curve similar to that seen when the blood was heparinized with Liqueamin Sodium 10.

Effect of Lipo Heparin and Liqueamin Sodium 10 on absorption of indocyanine green dye in citrated whole blood. Five out of six observations with Lipo Heparin used as the anticoagulant for fresh whole blood

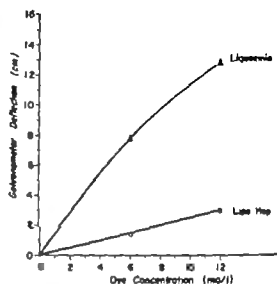


Fig. 1 Effect of Lipo Heparin and Liqueamin sodium 10 on the absorption of 800 mμ of light by indocyanine green dye in fresh whole blood. The optical densities of the blank blood as measured by the Waters NC 100A densitometer are 0.70 and 0.72 for Liqueamin and Lipo Heparin respectively. This indicates that the presence of these heparin solutions does not cause a nonspecific effect in the blank blood of a magnitude great enough to affect the calibration of the background-dye compensated NC 100A. However it does not rule out the possibility that a nonspecific effect may be present when Lipo Heparin, blood and indocyanine green are mixed.

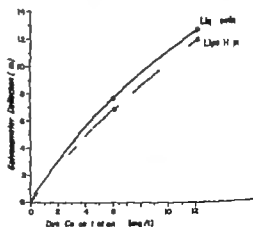


Fig. 2 Effect of Lipo Heparin and Liqueamin sodium 10 on indicator dilution calibration curves of indocyanine green dye in citrated blood. Little decrease in the absorption of light at 800 mμ is seen in the set of dye dilutions containing 0.2 cc of Lipo Heparin per 5 cc of blood-dye solutions.

*Organon Inc. W. 0808 M J

†Waters NC 100A densitometer manufactured by Waters Corp. Rochester, Minn.

‡Harvard syringe set at speed 3 with the use of 20-c syringe.

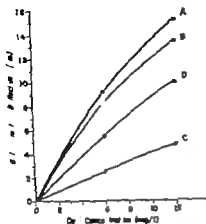


Fig. 3 Effect of various colorless solutions on absorption of indocyanine green dye in fresh whole blood. All sets of dye dilution contain laboratory prepared sodium heparin mixed with isotonic saline to a concentration of 1,000 units of heparin per cubic centimeter of solution. The optical densities of the samples of blank blood as measured by the NC 100A densitometer (peak sensitivity at a wave length of approximately 800 m μ) are: Set A = 0.77 B = 0.73 C = 0.75 and D = 0.75.

with no other additive present showed a decrease in light absorption. At no time was this marked decrease in absorption observed in our studies in which dye and Lipo-Hepan or Laqueamin Sodium 10 were added to citrated blood (Fig. 2).

Effect of various colorless solutions on absorption of indocyanine green dye in fresh whole blood. Lipo-Hepan unlike Laqueamin Sodium 10 contains 0.1 per cent sodium bisulfite in addition to the benzyl alcohol used as a preservative in both. Therefore benzyl alcohol and sodium bisulfite solutions were added separately to fresh blood dye mixtures of known concentrations and drawn through the densitometer in the standard method for calibrating the instrument. The anticoagulant used was laboratory prepared heparin* at a concentration of 40 units per cubic centimeter of blood.

The effect of these solutions on identical concentrations of dye blood solutions of 0.6 and 12 mg. per liter of dye concentrations is shown in Fig. 3. Curve A is the calibration obtained from the set of dye

dilutions to which 0.2 c.c. of distilled water per 5 c.c. of blood dye solution was added to keep the dilution the same for all solutions. This curve exhibited the greatest absorption of light as sensed by the densitometer. Slightly less absorption of light at a wave length of 800 m μ was seen when 0.2 c.c. of 0.9 per cent benzyl alcohol was added to each 5 c.c. of blood dye solution (curve B).

The addition of 0.2 c.c. of 0.1 per cent sodium bisulfite to 5 c.c. of blood dye dilution (curve C) resulted in a marked decrease in absorption. When 0.2 c.c. of 0.9 per cent benzyl alcohol and 0.1 per cent sodium bisulfite were added to 5 c.c. of solution a light absorption intermediate between B and C was found (curve D).

The spectral absorption of these additives as well as of Lipo-Hepan and Laqueamin Sodium 10 were studied from a wave length of 650 m μ to 1 μ and found to be very nearly the same as that of water. At wave lengths between 900 m μ and 1 μ benzyl alcohol transmits more light than water.

Effect of colorless solutions on absorption of indocyanine green dye. Speculation arose as to whether this reduction in light absorption at 800 m μ was due to a change in the structure of the dye molecule because of the presence of sodium bisulfite thus changing the wave length of peak absorption. Dye and distilled water solutions were made and combined with various colorless solutions used as additives. A water dye solution with the same dye concentration for all solutions was used as the control. As shown in Fig. 4 a marked decrease in optical density of the dye solutions was observed in the sample containing sodium bisulfite (curve D). A significant difference in optical density between the control sample (curve C) and the sample containing Lipo-Hepan (curve A) was not observed with a concentration of 0.2 c.c. of Lipo-Hepan in 5 c.c. of dye water solution nor were there any optical suggestions of either polymolecular aggregation or polymerization over the wave lengths studied.

Effect of time on indocyanine green dye in aqueous solution. An aqueous solution of indocyanine green in a concentration of 1.25 mg. per cubic centimeter kept un-

Heparin: crystal dissolved in isotonic saline to give concentration of 1,000 units per cubic centimeter.

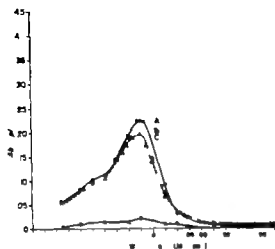


Fig. 4 Spectral absorption curves of dye and water solution with various colorless additives. Solutions are of 5 ml distilled water plus 0.006 cc of 1.25 mg per cubic centimeter dye (Hannan Westcott & Dunn special diluent used to dilute the dye) and 0.2 cc (added) of the spectral absorption curve for sample with 0.2 cc of Lipo H per added. Curves B and C represent absorption curves for sample containing 0.2 cc of Liqueurmin Sodium III and 0.2 cc of water (control) respectively, whereas D is the absorption curve observed for aqueous dye dilution containing 0.2 cc of sodium benzoate. Not that no appreciable effect is seen when Lipo H per is added to the dye water solution compared to that seen when water and Liqueurmin are used as a additive. However the addition of 0.2 cc of sodium benzoate (0.1 per cent) produces a marked decrease in light absorption at the wave length studied.

disturbed for 7 days was found to have shifted in maximal absorption from 740 to 900 mμ. Therefore it was decided to study the effects of time systematically.

Fresh solutions of a dye concentration of 1.25 mg per cubic centimeter were made using the special diluent⁸ furnished with the dye and kept at room temperature for varying lengths of time. Each day a sample of this dye was diluted with distilled water to a concentration of 1.5 mg per liter and its spectral absorption characteristics were studied between 630 mμ and 1 μ. Peak absorption of this concentrated dye solution remained at 780 mμ for 2 to 6 days although the absolute light absorption at this wave length decreased with time. The solutions studied developed a

second absorption peak at a wave length of 900 mμ sometime during the second through the seventh days in solution (Fig. 5). Within 1 to 3 days after its initial appearance the second peak markedly increased its absorption as shown by curve C of Fig. 5.

This shift in peak absorption of the dye in solution was also studied by comparing the effects of time and concentration. A concentrated solution (1.25 mg per cubic centimeter) was made with the diluent furnished with the dye by Hannan Westcott & Dunn and studied as previously described. In this case the concentrated sample showed a shift in peak absorption to 900 mμ on the sixth day. Light absorption of concentrated aqueous solutions (1.25 mg per cubic centimeter) aged as long as 9 months was also studied. In every case the peak absorption was found at 900 mμ instead of at 780 mμ.

Two aliquots were diluted with distilled water to a concentration of 1.5 mg per

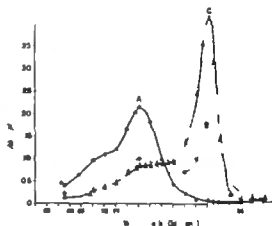


Fig. 5 Effect of time on sodium cyanine green dye in a concentrated aqueous solution. The dye was kept in solution of a concentration of 1.25 mg per cubic centimeter and diluted with distilled water to a concentration of 1.5 mg per liter for spectrophotometric study. Curve A is the observed spectral absorption curve for the dye water dilution on the same day that it was dissolved in the diluent. Curve B is the absorption curve for the dye in concentrated solution for 6 days and curve C was observed after the dye was in the 1.15 mg per cubic centimeter solution for 8 days. This shift in peak absorption to a longer wave length as a well documented phenomenon for cyanine dyes in aqueous solutions. It is thought to be due to polymolecular aggregation in an orderly array.¹⁰

The diluent used distilled water, due to its high purity, was found to be the best for the purpose of this study.

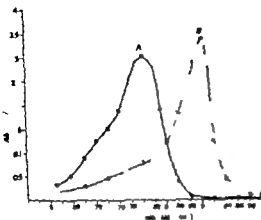


Fig. 6 Spectrophotometric observation of fresh and aged indocyanine green dye in plasma (dye concentration of 1.25 mg. per liter). Curve A is spectral absorption curve of fresh dye in plasma and curve B is an absorption curve of dye (aged 7 days in concentrated aqueous solution) in plasma.

liter Oxygen (100 per cent) was bubbled through one of the diluted samples for 10 hours at a rate of 2 L. per minute and the other sample was left undisturbed. Both solutions were studied hourly for 10 hours and then daily for a total of 7 days. Neither sample exhibited a shift in peak absorption but after 7 days both had optical densities essentially the same as that of water throughout the wave lengths of 650 μ to 1 μ .

Effect of aging of indocyanine green in plasma. Spectral absorption of fresh and aged dye plasma solutions was also studied (Fig. 6). Note that the peak absorption of fresh dye in plasma (Fig. 6 curve A) was observed at 600 μ a shift of 20 μ from the peak observed in water solution. This observed shift of peak absorption of the fresh dye from 780 μ (water solution) to 900 μ in plasma is in close agreement with previous studies by Fox and Wood.³ However peak absorption of the aged dye plasma solution was observed at 900 μ the same as that seen in the dye water solution (Fig. 6 curve B).

Discussion

Light absorption of indocyanine green dye in fresh whole blood is rendered ex-

tremely unstable and is often markedly decreased when Lipo Heparin is used as an anticoagulant. Because of these observations the practice of using Lipo Heparin as an anticoagulant for densitometer calibration of indocyanine green concentration has been discontinued at the University of Florida Teaching Hospital.

Even extremely small quantities of sodium bisulfite decrease light absorption of indocyanine green dye in fresh blood. A marked difference in the optical density of indocyanine green dye in the presence of a procaine solution also containing sodium bisulfite likewise occurs.⁴

When either Lipo-Heparin or sodium bisulfite is added to fresh blood there is essentially no change in the optical density of the blank blood. This does not rule out the possibility that a nonspecific effect is present when the dye is added to the blood heparinized with Lipo-Heparin. Spectrophotometric studies to date have not shown a shift in spectral absorption of the dye or a decrease in light absorption in the presence of Lipo-Heparin at a concentration of 0.2 cc. per 5 cc. of dye solution in either plasma or water over the wave lengths studied (650 μ to 1 μ) and with the concentrations of Lipo Heparin used.

Indocyanine green dye in a concentrated aqueous solution (1.25 mg. per cubic centimeter) shifts its peak absorption of light from 780 to 900 μ between the second and sixth days and then remains the same for at least as long as 8 months. Dilute aqueous solutions (1.5 mg. per liter) did not exhibit this shift in peak absorption but instead decreased light absorption to almost that of water.

Studies of indocyanine green dye in blood plasma have shown this dye to be bound by the plasma proteins specifically the albumin. The shift in peak absorption of the dye from 780 μ in water to 800 μ in plasma is additional evidence that this dye is bound to the blood albumin. Conversely therefore the absence of a shift in peak absorption of the aged dye solution in plasma is some evidence that the dye after polymolecular aggregation occurs is not bound to plasma proteins. However electrophoretic and ultracentrifugation studies on the aggregated dye in plasma have not been performed.

These observations of optical behavior of this dye in concentrated and dilute solutions with respect to time are in agreement with other studies of cyanine dyes in aqueous solution. The shift of peak absorption to a longer wave length is probably due to a reversible poly molecular aggregation¹ as discussed previously.

Summary

Indocyanine green dye in the presence of sodium bisulfite exhibits a marked and extremely variable decrease in light absorption. Even the presence of the extremely minute quantity present in Lipo Hepin when used as an anticoagulant will vitiate densitometer calibration.

Spectrophotometric studies of aqueous solutions of dye in the presence of Lipo Hepin do not show a marked change in light absorption of the dye. Stronger solutions of sodium bisulfite produced a marked decrease in light absorption over these wave lengths.

Indocyanine green dye kept in a concentrated aqueous solution for periods up to 7 days shifts its peak absorption from 780 to 900 m μ . This shift in peak absorption is probably due to reversible poly molecular aggregation.

As previously reported fresh solutions of indocyanine green in plasma have an absorption maximum at 800 m μ . Peak absorption of aged dye plasma solutions remains at 900 m μ .

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Computer interpretation of electrocardiograms

L F Staples MD*

J E Gustafson MD

G J Balm MS

W A Tate BA

Des Moines Iowa

The use of the digital computer in the interpretation of electrocardiograms can be a valuable tool especially to the noncardiologist physician. Physicians in general practice or those who practice general medicine often read an insufficient number of electrocardiograms to keep all of the subtle diagnostic criteria at hand and ready for use.

The computer program once stored in the computer is retrieved unerringly and as often as is requested and all quantitative aspects of the electrocardiogram are analyzed. The results are consistent and the computer is uninfluenced by anything other than the stored criteria. The physician is influenced by what is seen and on occasion may not see a second or third abnormality present and this is especially likely if the first one seen is of some magnitude. An example of this is shown in Fig. 1. Here it is obvious that the patient has an arrhythmia and that he has had a recent anteroseptal myocardial infarction. These were not missed by any of the physicians who read the tracing as an unknown but three of six physicians failed to note the changes of a posterior myocardial infarction as well. The computer diagnosed all three abnormalities (Fig. 2).

As part of a program designed to demonstrate the usefulness of the computer as an aid to diagnosis a 3 year project was undertaken to write a workable program, test its validity and establish its usefulness in a private nonuniversity hospital.

Methods and material

Initially, reasonable criteria for the various electrocardiographic abnormalities common, encountered in adults were selected. Programs were written to include all major abnormalities except certain of the arrhythmias. Electrocardiograms exemplifying these were selected and technicians were instructed how to measure exactly the various components of the tracings. Guidelines outlining the details of measurement were formulated and put into pamphlet form so that technicians could repeatedly refer to them in the interest of standardization in the handling of data.

As an example, the onset of the intrinsic Q deflection in Lead V₁ is measured from the onset of the QRS complex to the point at which the stylus begins to fall abruptly toward the isoelectric line (Fig. 3).

Measurement cards (Fig. 4) were then completed by the technicians for each

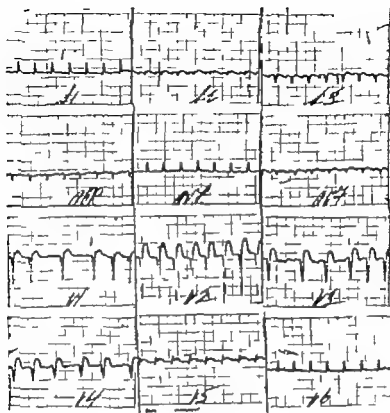


Fig. 1 See text

IOWA METHODIST HOSPITAL
 RAYMOND BLANK MEMORIAL HOSPITAL FOR CHILDREN
 TOWNES MEMORIAL REHABILITATION CENTER
 ELECTROCARDIOGRAPH (COMPUTER) INTERPRETATION

[REDACTED]				02 19-62 AECC			
75		0158					
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Fig. 2 See text

and S-T segment changes (abnormal or borderline) are searched for in the order indicated. The latter are omitted in the presence of bundle branch block or ventricular hypertrophy. Complete RBBB and complete LBBB are mutually exclusive and if either is diagnosed as being present RVH and LVH are not considered for purposes of this program.

In an effort to evaluate and validate the program currently in use in the computer 145 electrocardiograms considered to be reasonably typical examples of normal and abnormal tracings commonly encountered and which have been programmed were sent as unknowns to two university cardiologists and to six other internists.

Table I lists the tracings in which a significant difference of opinion existed between readers and the computer. Much of this is due to overreading, or to underreading, by the computer.

The six nonuniversity internists had major differences in diagnoses varying from thirty-four instances per physician with the average difference being sixteen.

Results

Four thousand four hundred and sixty-nine electrocardiograms have been analyzed by the computer. Each computer diagnosis was checked by one of the authors (H. H. S.) and each of the cardiograms was read by him in order to check computer accuracy. His diagnosis and that of the computer were in agreement except for nineteen electrocardiograms. Thirteen of these were considered to have been overread by the computer as posterior infarction and two as anterior infarction. In so far as has been possible consecutive electrocardiograms taken on patients make up the above number. Because duplicate copies of the electrocardiograms were not made for all patients some were lost to

Table I

Tracing number	Computer diagnosis	Physicians' diagnosis
11	Complete right bundle branch block	Right atricular hypertrophy
17	Anterior infarction and posterior infarction	Anterior infarction
45R	Complete right bundle branch block and posterior infarction	Complete right bundle branch block
10R	Left ventricular hypertrophy and anterior infarction	Left ventricular hypertrophy anterior infarction po.terior infarction
13R	Arrhythmia anterior infarction po.terior infarction	Atrial fibrillation anterior infarction
22R	Left atricular hypertrophy anterior infarction posterior infarction	Anterior infarction and po.terior infarction
23R	Anterior infarction posterior infarction	Anterior infarction
25R	Left ventricular hypertrophy anterior infarction	Left ventricular hypertrophy
50R	Atrial fibrillation right ventricular hypertrophy posterior infarction	Atrial fibrillation right ventricular hypertrophy
57R	Left atricular hypertrophy anterior infarction	Left ventricular hypertrophy
60R	Left atricular hypertrophy anterior infarction	Anterior infarction
102R	Right ventricular hypertrophy po.terior infarction	Incomplete right bundle branch block
104R	T and S-T abnormal	Anterior infarction
108R	Abnormal	Anterior infarction
111R	Anterior infarction posterior infarction	Anterior infarction
114R	Left atricular hypertrophy anterior infarction	Left atricular hypertrophy
126R	Right ventricular hypertrophy po.terior infarction	Anterior infarction
145R	Atrial fibrillation po.terior infarction	Atrial fibrillation left atricular hypertrophy posterior infarction

Table II Computer diagnosis of 4169 electrocardiograms

Number of tracings	Diagnosis	Number of tracings	Diagnosis
469	Normal	1244	Within normal limits
157	Tachycardia	1334	Abnormal T wave
861	Abnormal S-T segments	238	Atrial fibrillation
10	2nd or 3rd degree A-V block	5	Wolff Parkinson White syndrome
164	1st degree A-V block	71	Short P-R interval
32	Intraventricular conduction defect	373	Prolonged Q-T interval
Ventricular Hypertrophy			
9	Right	93	Left
39	Possible	171	Possible
9	Probable	77	Probable
Bundle Branch Block			
116	Complete right	39	Complete left
34	Incomplete right		
Myocardial Infarction			
	Posterior (diaphragmatic)		Anterior
21	Acute	36	Acute
42	Evolutionary	61	Evolutionary
234	Old	268	Old
78	With lateral extension		

the project. However, the tracings taken are considered to be representative of a cross section of those taken in a large general hospital population with acute conditions. Table II shows the distribution of the diagnoses as printed by the computer.

Within normal limits includes tracings with minimal tachycardia, bradycardia, minimal prolongation of the P-R interval, borderline Q-T interval, borderline T wave, and borderline S-T segment changes if these were the only diagnoses made on the tracings. Second degree and third degree A-V blocks were diagnosed categorically when the atrial (P wave) rate was more rapid than the ventricular (QRS) rate (premature atrial contractions excepted). No attempt was made to separate second degree from third degree A-V block in this program.

Posterior infarction with lateral extension was diagnosed whenever, in addition to Leads II, III, and aVF, appropriate changes were also seen in Leads V₄ and V₆.

In 155 tracings abnormalities of the T wave only were diagnosed, and in only 20 cases was the diagnosis abnormal S-T segment only. In 151 electrocardiograms

the combination of abnormal T wave and S-T segment only was diagnosed.

Comments

In a very short time after the start of the project it became apparent that changes had to be made in the manner in which usual criteria were handled in order to adapt them to a computer program. Criteria are weighted in formulas which can be adjusted to correct for underreading or overreading a particular abnormality.

As an example, the left ventricular hypertrophy program assigns varying weight to the R wave amplitude in Lead V₁ or Lead V₂, Lead aVL, or Lead aV₁, and to the T wave in Lead V₁, the latter being influenced also by the amplitude of the R wave in Lead V₄. Weight is also given to a negative S-T segment. A scale is set up and in terms of the sum of the product from each of the formulas a decision is made whether left ventricular hypertrophy is or is not present and if it is whether it is possible, probable, or definite (marked) (Fig. 7). Similar formulas are used in deciding on the presence or absence of right ventricular hyper-

Page 2 AFCH

VII Y tri lar hyper trophy (Don't check RV6 or LV6 if QRS or TQRS is present)

A Left

- 1 (RV6 18)4 or (RV5 20)4 (Use greater of 2 products)
- 2 (RV1 8)2
- 3 (intrinsoid V6 048) (180) (8)
- 4 (1 RV6 TV6) (8) (RV6) (If TV6 < -2 make it = -2)
- 5 (R VL 18)3
- 6 (RdV 20)3
- 7 (1 RdV TdV) (2) (R V6) (Only if RdV and RV6 are > 18)
- 8 (R RT V6) (If RT V6 < 8)

B Criteri

ARI	ROPE	POE 1 LI	PROE 0LE	DEF (TV MARKED)
> 33	30 40	50 70	T1 90	> 90
< 33	40 60	60 80	33 180	> 100

Fig 7 See text

trophy complete and incomplete right bundle branch block and complete left bundle branch block. A cardiologist who wishes to emphasize amplitudes of R waves or to make the program more sensitive may simply change a factor in the appropriate formula.

Myocardial infarctions are handled through generally accepted criteria. The electrocardiographic age of an infarct is determined by ST segment elevation and by the depth of T wave inversion. It is recognized that this can at best be an approximation since serial comparison is not performed in the present program. Old posterior infarctions have given considerable difficulty because of the absence of clear cut criteria especially in low voltage tracings.

One of the drawbacks of the program in its present form is that a considerable amount of time must be spent in teaching technicians to do the measurements properly. Also a skilled technician requires on the average 10 minutes to make the appropriate measurements. These must then be transferred to cards as indicated earlier. The total time required to completely process each electrocardiogram including a printed diagnosis from the computer is about 11 minutes. In order to circumvent measurement by a technician and to shorten the time required for processing and in order to make possible direct transmission of analogue data

to the computer an FM tape program is presently in the developmental stage.

Summary

The use of the digital computer in the interpretation of electrocardiograms seems to offer assistance especially to the non cardiologist physician. To test this thesis a 3 year project was undertaken to write a workable program test its validity and establish its usefulness in a private non university hospital. This paper presents the factors involved in the programming and the problems encountered.

Our experience indicates that computer interpretation of electrocardiograms is successful. Although the input of most of our material has been from hand measurements by a technician the program also works on electronically converted data.

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Coronary inflow after systemic-to-coronary artery anastomosis in dogs

Hans H. Scheldt M.D.*

Harm Krause Ph.D.

Berlin Germany

Because of the fact that the morbidity and mortality of stenosing coronary diseases recorded in the statistics on heart troubles have been increasing at an alarming rate in almost all industrialized countries since World War II therapy research in this field has been intensified during the last decade. Since the prerequisites for a coronary dilating collateral circulation inducing effect by drugs are mostly limited in the case of advanced structural lesions of the walls with a reduced flexibility and high grade narrowing the demand for adequate surgical measures to be applied to such patients is becoming more urgent.

Whereas *indirect* methods for the revascularization of the ischemic myocardium such as cardiopexy with extracardiac structures containing vessels hyperemia of the cardiac surface by producing a sterile epicarditis internalization of the coronary venous system implantation of the internal mammary artery into the myocardium or bilateral ligation of the latter have not yet yielded any convincing results in animal experiments and in clinical practice *direct* surgical interventions on the coronary arteries appear to promise more success in so far as the segmental stenoses of main branches are concerned. In addition

to efforts made toward removing stenoses of the lumen by curettage endarterectomy and dilation of the stenotic ring by means of a patch graft numerous experiments have been aimed at overcoming the segmental narrowing by creating an anastomosis between an arterial branch of the aortic arch and the coronary stem beyond the stenosis. The shunting was made via mobilized arteries¹⁻⁴ arterial or venous vascular grafts^{5-10,12,13} or prosthetic vessels.²⁻⁴ Although such experiments have partially led to satisfactory laboratory results a clinical application has hitherto been condemned to failure because of the high percentage of thromboses occurring in the vascular shunts of small caliber. This may well account for the fact that so far experimenters in this field have almost invariably confined themselves to the surgical problem of the suturing technique to be applied whereas the functional behavior of anastomoses was dealt with merely in a general clinical respect. Thus no publication yet exists which describes the peculiar hemodynamic conditions in systemic-to-coronary artery anastomoses.

This paper reports on experiments in which the coronary inflow in dog hearts was examined prior to and after the shunting with systemic arteries.

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Address: Department of Experimental Cardiac and Vascular Surgery, German Academy of Sciences, Hospital am Friedrichshagen, Berlin 1017, Germany.

Methods

The studies were performed on 25 mongrel dogs weighing 24 to 28 kilograms. Morphine was applied as a preanesthetic and anesthesia was induced with sodium barbital (approximately 30 mg per kilogram). The respiration was maintained by means of a mechanical insufflator via a cuffed endotracheal tube using fresh air. The thorax was opened in the fifth left intercostal space with the animal on its right side. After the pericardium had been opened above the auriculoventricular sulcus the circumflex branch of the left coronary artery was exposed from its origin to the site of branching of the ramus marginalis obtusior. This resulted in a segment of about 4 cm in length which was freed from small tributaries as well as from the ramus descendens ventriculi sinister. If the latter was of large size which would have meant the formation of an extensive area of infarction the animal was used for other experimental purposes. The main branch to the septum and the proximal auricular branch were carefully spared. The coronary anastomosis was performed with the left subclavian artery mobilized directly or via the left internal mammary artery or a rubber tube having a 3 mm inner diameter which was joined with the left subclavian artery at the site of branching of the mammary artery via a short prosthetic tube of the same diameter. The wall of this model vascular tube was shaped in such a fashion that in the coronary region of measurement identical formal criteria of the pressure and flow pulses were fulfilled as in shunting with the subclavian artery or mammary artery so that similar volume elastic effects could be assumed in the arterial pressure region. After the vessels selected had been dissected free the dog was heparinized intravenously in order to maintain a constant level (initial dose 7 mg per kilogram).

The anastomosis was applied to the normally beating heart using a thin walled brass tube the diameter of which was adapted to the smallest of the two shunting vessels (varying in these experiments between 2.2 and 3 mm) and the length of which was 18 mm. This tube served at the same time for both pressure and flow measurements according to the differential

pressure method. For this purpose it was provided with two lateral pipes 0.8 mm in diameter and 10 mm in length which were attached 8 to 10 mm apart and connected each with the measuring chamber of Statham 123Cb transducers via flexible elastic tubes. The transmission of pressure from the blood channel to the recipient membranes of the strain gauges was thus accomplished through the lateral pipes, the elastic tubes and the measuring chambers of the transducers; this system was filled with physiologic saline free of bubbles. With the given diameters of the measuring tubes the distance of 8 to 10 mm between the pipes was sufficient to obtain measurable pressure differentials with arterial blood speeds. The pressure differentiation was accomplished by compensation of the two Statham transducers which were of similar pressure sensitivity. The flow zero was determined mechanically by means of two three-way stopcocks which were arranged between the elastic tubes and the measuring chambers and which could be changed over in such a way that the strain gauges became adjusted to atmospheric pressure and the column of fluid between the blood channel and the transducer was simultaneously interrupted. The natural frequency of the manometric system amounted to 500 cps.

Since the pressure and inflow conditions of the left circumflex artery had to be examined alternatively for comparison under original and extracardiac blood supply the anastomosing measuring tube had to be shaped in such a manner that it could connect the peripheral portion of the coronary artery with both the central portion and the systemic hunting vessel. The measuring tube used consisted of two parts each provided with a lateral pipe and fitted into one another by means of a gap less joint. The two parts when fitted together formed the measuring tube of the above stated dimensions. The central component tube existed in duplicate, one being inserted into the extracardiac shunting vessel and the other into the central portion of the coronary artery. Thus it was possible to adjust the pathway of the coronary blood supply as desired by a simple plugging over of the peripheral component tube to one of the two others; the free supply artery was

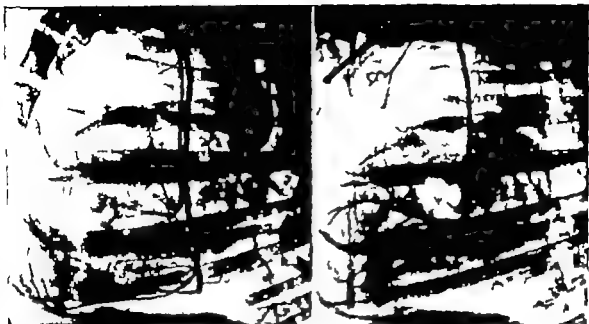


Fig 1 Angiograms of a dog with coronary anastomoses between the left mammary artery and the left circumflex artery (—) as well as between the right mammary artery and the anterior descending artery (---) using polyethylene prostheses. The control examination was performed on the regularly beating heart 8 months after the operation. The left arteriogram shows a retrograde filling of the right coronary artery.

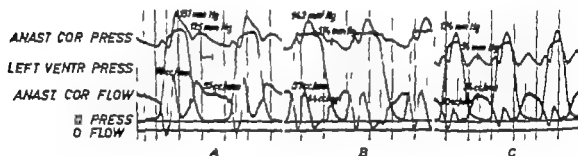


Fig 2 Original curves of pressure and flow of systemic to left circumflex artery anastomoses with low flow resistance (A) and high flow resistance (B, C) (For details see text) Indicated time interval = 100 msec.

Results

Fig 2 reproduces original curves of pressure and flow of anastomoses applied between the subclavian artery (A) or the internal mammary artery (B, C) and the left circumflex branch. To label the differences as compared to the original pressure and flow curves of the coronary artery concerned the equilibrated coronary oscillations which had been recorded immediately before or after shunting or during the latter—the respiration as shallow as possible—and which showed con-

gruent pressure curves of the left ventricle have been synoptically demonstrated in Fig 3. As is shown by the prototype curve segments in A after retardation of the anastomotic pulse wave is compared to the onset of ventricular ejection the throttling of the early systolic inflow as well as the mid systolic forward flow are increased. After the maximum systolic flow had been reached the anastomotic coronary pressure rises above the ventricular pressure at the same time the speed abruptly decreases. Coincident with the



Fig. 3 Reproduction and comparison of original pressure and flow curves recorded prior to and after application of systemic to-left circumflex artery anastomosis having a sufficient (A) and a too narrow (C) lumen. Black arrows: Anastomotic additional inflow. Hatched areas: Loss of anastomotic flow as compared to the normal coronary inflow.

closure of the aortic valves and onset of isometric relaxation an acceleration of flow as well as a decline in pressure are to be recorded during the anastomotic coronary main wave. Along with the onset of the anastomotic diastolic wave we observed a second acceleration of blood lasting longer than the preceding one and leading to a stronger diastolic initial filling of the coronary artery. In the further process of diastole both pressure and flow curves that were recorded became approximately similar to each other.

In order to permit a better understanding of curves B and C of Fig. 2 we should like to explain these changes in pressure and flow first of all on the basis of the hemodynamic interrelationship between the pulse wave of the systemic artery which is transported to the left ventricle on a detour the starting pulse in the aorta and the changes in peripheral resistance in the myocardial cycle. Since the final diastolic pressure of the extracardiac anastomosis is reached only during the output period in increasing pressure gradient from the aorta to the coronary artery is recorded upon the onset of ejection from the left ventricle. This gradient counteracts the deceleration in flow of early systole which is favored by the long and elastic vascular tube of the anastomosis and moreover effects an additional acceleration of blood upon arrival of the anastomotic main wave. Upon discontinuance of the accelerating effect of the gradient at the point of inter-

section of ventricular or aortic pressure and anastomotic pressure the high speed is suddenly discontinued too. This in turn leads to a further rise in pressure since the flow pressure acts as an additional static pressure right here. The inversion of the aorto-coronary pressure incline resulting therefrom leads to a brusque diminution in flow. The subsequent myocardial relaxation starts prior to the end of the anastomotic coronary main wave. Since the blood flow of the shunt artery is slowed down at this time only a partial volume can be accelerated with a simultaneous drop in pressure. The retarded diastolic wave meets this partial volume. Thus the volume is accelerated twice. The efficiency of this acceleration is diminished however by the fact that a centripetal pressure gradient exists between the aorta and the coronary artery even during protodiastole. This leads to an approximation of the anastomotic and original coronary inflow volumes already existing in mid-diastole.

These mechanism of an increased initial filling can however become effective only if the resistance of the shunt vessels is small enough to supply the quantity of blood required within the shortest possible interval. Such a prerequisite does not exist in experiments B and C of Figs. 2 and 3. Whereas only a moderate delay of the inflow is demonstrated in B the curve segments in C show a considerable insufficiency of the anastomotic volume capacity with a strong decline in pressure in early diastole.

So as to be able to estimate the influence of the distance of the shunt pathway upon coronary inflow the planimetry values of the anastomotic flow curves and the corresponding time values of the aorto-coronary pulse retardation ascertained by 74 individual measurements made in 6 suitable dogs were put into relationship with one another. Three of these animals belonged to an experimental series in which the model vascular tube with an internal diameter of 3 mm was inserted between the origin of the left internal mammary artery and the left circumflex branch being systematically shortened after each double measurement. The other 3 dogs were taken from a second experimental group in which analogous measurements were made. Here the mammary artery served as the shunt vessel. As for the physical parameters which may upon simultaneous change the coronary inflow in the reproduction experiments having a regular supply of oxygen to the myocardium these above all had to be approximately constant: the aortic and coronary venous pressure, the systolic and diastolic inflow periods, the coronary inflow under natural conditions as well as the coronary resistance which can be estimated from the mean diastolic aortic pressure minus the critical closing pressure and the myocardial circulation per minute per 100 grams.¹ The mean duration of a cardiac cycle approximated 223 msec (± 3.8 per

cent). The diastolic aortic pressure effective for the coronary perfusion ranged from 75 to 79 mm Hg with amplitudes from 37 to 42 mm Hg. The mean coronary sinus pressure amounted to 8.8 mm Hg ± 9 per cent (max) or 2.1 mm Hg ± 28 per cent (min) respectively under natural arterial inflow conditions so as to partly rise again after application of the anastomosis. (The behavior of the coronary venous blood flow in the case of extra-cardiac anastomoses is now being investigated in detail.)

The time-volume relationships of the anastomoses with the model vascular tubes (a) and with the mammary artery (b) are graphically demonstrated in Fig. 4. The ordinates state the percentage surface difference as compared to the original coronary flow curve; this comparative value is assumed to amount to 100 per cent. It turned out that in both experimental groups the systolic inflow was relatively more strongly affected by retardation of the anastomotic pulse wave than by the diastolic blood flow. Because of the considerable acceleration of blood in mid-systole the blood flow recorded during the output period in the tubes amounted to a pulse lag of 55 msec and in the narrow lumen arteries pulse lags of 36 to 43 msec above the corresponding coronary value. Only after these times have been exceeded does the prolonged duration of the early systolic throttling of the blood flow have a

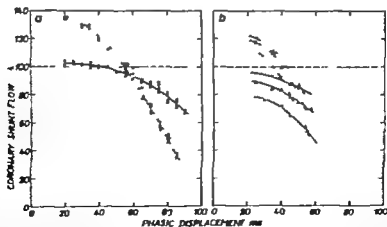


Fig. 4. Graph indicating, as percentage, the changes in flow of coronary to-systolic artery anastomoses in systole (dashed lines) and in diastole (solid lines) with different phase displacement between the pulse waves of the aorta and those of the coronary artery. a. Anastomoses with low flow resistance. b. Anastomoses with high flow resistance.

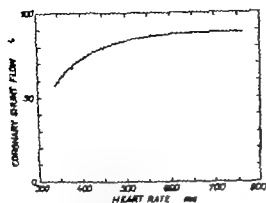


Fig 5 Diagram on the relative changes in flow of an retrocardiac coronary anastomosis with a too small diameter at a varying heart rate

more significant effect and finally become preponderant in an exponential ratio. In diastole the twofold acceleration of blood may lead to a slightly increased inflow under conditions of a minor lag and a sufficient cross section despite the retardation of the second rise. If the time difference exceeds 42 msec an exponential diminution in flow is recorded. If the cross section is too narrow above all the diastolic flow in long shunt pathways is considerably reduced.

The diagram of Fig 5 illustrates the dependence on frequency of the anastomotic blood flow with an insufficient cross section of the shunt artery. The changes in frequency have been thermally effected by cooling and heating of the sinusatrial node. In the graph the surface values of the total coronary inflow recorded prior to and after application of the shunt under conditions of adequate cardiac cycles (after a steady state has been established) are compared with regard to their percentage. With a rise in frequency the increase in the difference in flow recorded in the physiologic range is relatively insignificant. Only at a higher stroke rate does this difference in flow increase more markedly. This results in a prolonged systolic period per minute and a corresponding decrease in diastole. The diastolic ventricular pressure and the coronary sinus pressure did not undergo any significant change.

Finally the inflow of a mammary coronary anastomosis with a sufficient anastomotic volume capacity under conditions of

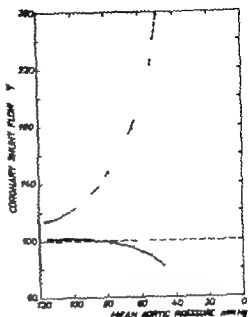


Fig 6 Opposite changes in the systolic (upper curve) and in the diastolic (lower curve) coronary inflow with a decline in the aortic pressure. Phase angle 22 degrees

physiologic pressure and frequency was examined in analogous comparative measurements with a spontaneous decline in the aortic pressure. This situation arises in prolonged experiments when the development of pressure in the heart is finally reduced because of myocardial fatigue. As a consequence the early systolic throttling of the blood flow is decreased while a relative increase in the mid systolic forward flow is recorded. Upon a more marked decline in pressure we observed a considerable drop in diastolic blood flow. This shifting with regard to the relationship between systolic and diastolic inflow in favor of systole is demonstrated in Fig 6.

Discussion

As is shown by the values recorded the blood flow of a systemic artery that is shunted to the heart is subject to phase changes similar to those of blood flow in the coronary artery. Basic differences at the beginning of the systolic and diastolic inflow can be analyzed from the lag between the pulsatile blood supply and the rhythmic changes in coronary resistance. They are quantitatively influenced by the degree of the phase angle of the anasto-

motus pulse wave as compared to the contraction cycle of the left ventricle as well as by the formation of alternating aorto coronary pressure gradients. In systole the phase-dependent delay in filling is overcompensated by a strongly blood accelerating anastomotic pressure gradient thus being associated with a high pressure and flow load of the shunting vessels. The increase in diastolic inflow arising from the volume acceleration effected twice is more favorable in a hemodynamic respect. Both factors may increase the total coronary inflow under given mechanical conditions. This respective observation is in agreement with the results published by Lord and co-workers.²⁰ At the time of comparative measurements of the coronary venous outflow prior to and right after the application of a subclavian to coronary artery anastomosis they obtained higher values in the case of shunting.

The length of the extracardiac shunt pathway is of decisive importance for the coronary inflow rate. The ventriculo-coronary phase angle as well as the flow resistance in the vessels of small caliber depend on this distance. If the cross section is big enough a prolongation of the bypath leads to an exponential decrease in the systolic and diastolic inflow due to the increasing delay of initial filling. This effect of a time-condition deficient inflow is intensified by a resistance induced filling insufficiency in the case of vascular lumina which are too narrow.

This combined flow inhibiting effect was observed in most cases of anastomosis of a coronary artery with the internal mammary artery which is preferably used in the experimenters²¹ because of its location near the heart. Adequate care and replacement by way of collateral vessels. Notwithstanding this fact the functional behavior of such shunts in surviving animals has so far been described as being sufficient. Here the angiographic detection of the anastomosis, the absence of symptoms of hypoxemia in the electrocardiogram and the maintenance of a normal exercise tolerance have served as evidence of a sufficient myocardial perfusion in the anastomotic region.^{11,12,13} We are able to confirm these clinical findings even after the application of a stenosing nonsuture technique with

rigid rings. However, as has been proved by radiographic checks and postmortem vascular visualization the decreased supply of coronary blood is compensated for by intercoronary anastomoses (Fig. 1). Obviously the development of a functionally efficient collateral circulation can be promoted by regular physical loading of the dogs. As may be seen from the symptomatic curves of Figs. 5 and 6 the inflow from the primary artery anastomoses may drop to critical values in the acute experiment if a stronger increase in frequency or a drop in the arterial systemic pressure is recorded.

When judging the respective results one must give due consideration to the fact that the phase pressure and flow courses were demonstrated on mobilized coronary branches located on the myocardial surface and thus were affected by pendulum oscillation of the pulse waves and volume elastic changes in vascular capacity. We think however that the results are of comparative value with reference to the actual intramural flow conditions. Although the relatively wide lumen anastomoses with the subclavian artery may equal or even exceed the original reference data with pulse lags up to about 40 msec the underlying compensating mechanisms constitute over a longer time period a dangerous vascular load and are thus in fact unphysiologic. It is also presumable that the considerable prolongation of the coronary inflow tract leads to an increasing danger of thrombosis because of the higher vascular resistance. Therefore an artificially changed coronary blood supply can be economical only if the surgeon endeavors to create the shortest possible external circulatory system. This had already been attempted in 1957 by Julian and associates² and later by Daicoff and associates³ and DeBakey²² who implanted a short homologous artery graft or prosthetic vessel between the ascending aorta 2 to 3 cm above the valve and the main branches of the coronary artery.

Summary

In acute experiments with thoracotomized dogs we determined the inflow into the circumflex branch of the left coronary artery by comparison under original flow

conditions and after anastomosing with systemic arteries of varying length and cross section using the left subclavian artery, the left internal mammary artery or in lieu of the latter model vascular tubes with similar elastic properties.

As has been proved, the prolonged path way of the coronary pulse wave and the resistant and accelerative forces of the left ventricle lead to both a systolic and a diastolic initial deficiency of filling and to a subsequent additional inflow as compared to the natural coronary flow. Provided that the cross section of the extracardiac shunting vessel is sufficient, the algebraic difference between both values depends on the degree of the phase displacement between the onset of the ventricular output period and the arrival of the coronary pulse wave on a detour. In the present experiments the ventriculo-coronary or aorto-coronary phase angle required for an adequate systemic-to-coronary artery inflow was below 38 degrees (3 msec) for systole and below 29 degrees (42 msec) for diastole. When these values are exceeded, the inflow drops in the shape of an exponential function.

When the internal diameter of the extracardiac shunting vessel was too small (below 2.5 mm) then the mid-systolic and protodiastolic inflows were reduced even with the shortest possible by-path between the subclavian artery and the coronary artery, causing a reduction in the total inflow rate in comparison with the natural values. In the chronic experiment the physiologic range of regulation of the coronary system with such anastomoses can however be maintained by the formation of compensatory collateral channels.

A strong rise in frequency and a spontaneous drop in arterial pressure may lead to a critical insufficiency of flow in the systemic-to-coronary artery anastomoses of small caliber.

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Case reports

Cardiac tamponade after transmynocardial extravasation of contrast material

Vasouchehr Nadimi MD*

Lampis D Anagnostopoulos MD *

Martin J Frank MD***

Jersey City, N J

Among the various complications that follow angiocardio-graphy are arrhythmias¹⁻⁴ allergic reaction to contrast material^{5,6} hypotension and circulatory collapse⁷ pneumothorax and pleural effusion⁸ pulmonary infarction and parenchymatous changes in the lung⁹ endocardial trauma¹⁰ perforation of the heart¹¹ coronary ischemia occlusion and myocardial infarction^{2,4,12} and extravasation of contrast material into the myocardium or pericardial sac^{1,13,14}

Although extravasation of contrast material into the myocardium or pericardial sac during angiocardio-graphy has been reported by many authors the outcome of this complication has varied. Cardiac tamponade^{15,16} and death⁶ have occurred in some patients whereas others have fully recovered without special treatment^{1,14}. Despite the frequency and seriousness of this complication the cause of tamponade and the factors responsible for a variable outcome have not yet been investigated. The purpose of this communication is to report a case in which

tamponade occurred after the transmynocardial extravasation of contrast material to report the result of animal studies performed to investigate the mechanism of tamponade that followed the entry of contrast material into the pericardial sac and to suggest a program for the management of patients in whom this complication occurs.

Case report

A 58-year-old white woman was admitted to the Thomas J. White Cardiopulmonary Institute for cardiac catheterization. Physical examination, chest films and electrocardiogram were compatible with rheumatic heart disease with mitral stenosis, mitral regurgitation and aortic stenosis. Routine laboratory examinations including bleeding clotting and prothrombin times were within normal limits. The hematocrit was 40 per cent.

On Oct. 8, 1964, the patient underwent a standard right and retrograde left heart catheterization to demonstrate the extent of the respect a. Aortic valve area gradient of 27 mm Hg. was found across the aortic valve and gradient of 10 mm across the mitral valve. For demonstration of the severity of mitral regurgitation cineangiograph was performed. At 1:00 p.m. 50 ml of 85 per cent Hyspaque (brand of sodium diatrizoate) was injected into the

* From the Department of Cardiology, Jersey City Medical Center, Jersey City, N.J.

*** From the Department of Cardiology, Jersey City Medical Center, Jersey City, N.J.

From the Department of Cardiology, Jersey City Medical Center, Jersey City, N.J.

From the Department of Cardiology, Jersey City Medical Center, Jersey City, N.J.

From the Department of Cardiology, Jersey City Medical Center, Jersey City, N.J.

left ventricle through a No. 6F NIH catheter by a Gidlund pressure syringe at a pressure of 8 kilograms per square centimeter. Immediately after injection the operator noted that approximately 80 per cent of the contrast material had entered the pericardial sac rather than the left ventricle and the patient complained of severe precordial pain. Recorded pressures showed a normal left ventricular contour without hypotension. Intermittent fluoroscopy over the next 70 minutes revealed gradual expansion of the pericardial space which was well outlined by the contrast material. At 2:30 P.M. the patient became cyanotic and hypotensive with a systolic pressure of 70 mm Hg and pulsus paradoxus. Over the next 2 minutes the peripheral pulses became impalpable and the blood pressure unobtainable. At 2:32 P.M. under fluoroscopic guidance a special pericardiocentesis was performed and 118 ml of bloody fluid was withdrawn. The fluid was found to have a hematocrit of only 5 per cent. Immediately after the removal of the fluid the signs returned to normal and the cardiac silhouette became smaller. However 40 to 50 per cent of the original amount of estimated pericardiocentesis fluid was still visible fluoroscopically. No further attempt at aspiration was made because the present condition was markedly improved and ventricular irritability resulted from contact of the aspirating needle with the myocardium. Vital signs remained normal throughout the night and a chest x-ray film taken the next morning failed to demonstrate residual contrast material in the pericardial sac.

Comments

A pericardial fluid hematocrit of only 5 per cent appears to indicate that hemorrhage was not the cause of tamponade in this patient. Since Hypaque in the concentration used has an osmolality in excess of 2500 mOsm per liter whereas plasma osmolality is approximately 320 mOsm per liter¹⁷ it was thought that a possible explanation for the occurrence of tamponade was the extrusion of serous fluid from the epicardial and pericardial surfaces into the pericardial space. This hypothesis was tested in a series of animal experiments designed to evaluate the effect of contrast material injected directly into the pericardial sac.

Materials and methods

Eight adult mongrel dogs weighing from 20 to 25 kilograms were anesthetized with intravenous sodium pentobarbital (25 mg per kilogram) supplemented as required to maintain moderate anesthesia. After the insertion of an endotracheal tube respiration was maintained with a

Harvard respiratory pump. Catheters were positioned in the right and left ventricles via the external jugular vein and carotid artery respectively. The chest was opened in the fifth intercostal space and the pericardial sac was cannulated with an open polyethylene tube (I.D. 1.13 mm). The polyethylene tube was brought out through the corner of the incision, the chest was closed and the lungs were inflated. Left and right ventricular pressures and Lead II of the electrocardiogram were monitored continuously on a photographic recorder (Electronics for Medicine) using Statham P23Db strain gauges. After control recordings were obtained 65 per cent Hypaque in amounts varying from 0.5 to 1.5 ml per kilogram of body weight warmed to body temperature was injected into the pericardial space through the tubing. Heart rate and left and right ventricular pressures were monitored continuously and recorded intermittently over the ensuing period of observation. The absence of leakage of dye from the sac was confirmed by frequent fluoroscopy. These observations also served as a semiquantitative method of evaluating the volume of fluid in the pericardial space. At the termination of each experiment the pericardial fluid was withdrawn and the volume measured. In 4 animals the osmolality of both the injectate and the withdrawn pericardial fluid was determined by freezing point depression after serial dilutions with distilled water.¹⁸

Statistical analyses were performed with conventional methods for small samples. Differences were evaluated by Student's *t* test. Correlations were measured with the correlation coefficient *r*.

Results

The effects of the injection of contrast medium into the pericardial sac are summarized in Tables I and II. The amount of contrast material injected ranged from 9 to 25 ml with a mean of 16 ml. The volume of the pericardial space as seen by fluoroscopy markedly increased in all cases. The x-ray films in Fig. 1 illustrate the size of the pericardial sac immediately after the injection of contrast material and 90 minutes later in Dog No. 7. In Dog No. 8 the pericardial fluid leaked out into the

Table I Osmotic effects of the injection of contrast medium into the pericardial sac

Dog No	Dose (ml/kg)	Time interval for maximum effect (min)	Volume of dye injected (ml)	Final volume (ml)	Initial osmolality (mOsm/L)	Final osmolality (mOsm/L)
1	0.5	149	9	35	2 866	433
2	0.6	97	10	65	2 000	470
3	0.7	109	14	88	—	—
4	0.8	167	16	10	2 670	326
5	1.0	94	18	85	2 670	354
6	1.5	117	24	110	—	—
7	1.5	26	23	107	—	—
8	1.5	134	25	Leaked out	—	—
Mean values		112 ± 42.9	16 ± 5.8	88 ± 21.4	2 551 ± 379.1	383 ± 51.5
Significance of differences			p < 0.01		p < 0.01	

Table II Hemodynamic changes produced by the intrapericardial injection of contrast material

Dog No	Heart rate (beats/min)	Pressures (mm Hg)			
		L1 SP	L1 EDP	R1 SP	R1 EDP
1	120 170†	130 90	8 7	25 26	6 4
2	152 160	136 121	3 4	31 24	4 4
3	160 170	185 121	6 10	30 41	8 8
4	170 174	196 91	11 21	41 49	7 16
5	106 96	206 146	9 17	34 33	9 3
6	186 275	118 109	5 10	30 35	4 10
7	150 170	87 59	2 5	23 28	2 3
8	132 110	162 127	7 11	34 24	2 8
Mean control values	147 ± 26	152 ± 41	6.4 ± 3	31 ± 5.6	5 ± 2.6
Mean final values	154 ± 40	108 ± 7	10.6 ± 5.8	37 ± 8.9	± 4.5
Significance of differences	p < 0.5	p < 0.01	p < 0	p < 0.8	p < 0.3

*Control value.

†Final value.

L1 SP Left ventricular systolic pressure L1 EDP Left ventricular end-diastolic pressure R1 SP Right ventricular systolic pressure
R1 EDP Right ventricular end-diastolic pressure

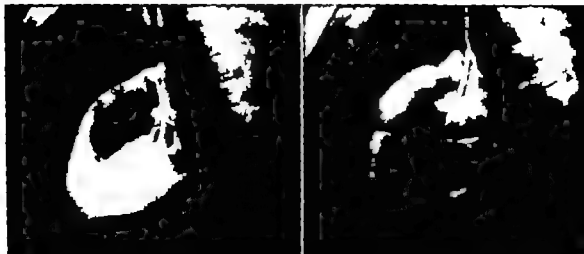


Fig. 1 The appearance of the pericardial sac after the injection of contrast material. The x ray photograph on the left illustrates the appearance of the pericardial space immediately after injection of 23 ml of contrast material and the x ray film on the right 90 minutes later in Dog No. 7.

chest cavity after massive expansion of the pericardial sac and therefore the final volume of fluid accumulated could not be measured. The amount of pericardial fluid withdrawn at the end of each experiment ranged from 55 to 110 ml with a mean of 88 ml, an increase of 550 per cent ($p < 0.01$). For the 4 animals in which measurements were made the average osmolality of the injectate was 2522 mOsm per liter and of the fluid withdrawn 383 mOsm per liter. This indicates significant dilution by solute free water. The final osmolality is still somewhat above that found in normal dogs in this laboratory (290 to 300 mOsm per liter). If it is assumed that none of the injectate had left the pericardial sac via capillary and lymphatic drainage the mean final volume in these 4 animals would have been 88 ml. Since the mean final volume was 13 per cent less than expected this suggests that a part of the injectate was removed by the vascular or lymphatic systems and that passage across this membrane was bidirectional. However in all animals residual pericardial fluid which could not be recovered was present.

The time interval necessary for the maximum osmotic and hemodynamic effects to occur ranged from 94 to 167 minutes with the exception of Dog No. 7 in which the time was 26 minutes. This

animal was hypotensive prior to the injection of contrast material (Table II). There was a good correlation ($r = 0.89$, $p < 0.01$) between the volume of contrast material injected and the amount of pericardial fluid withdrawn. However it is of interest that there was no correlation between the volume of the injectate and the time required for maximum effect to occur ($r = 0.30$, $p < 0.3$).

The hemodynamic changes produced by the injection of contrast material into the pericardial sac are summarized in Table II. Mean heart rate did not change significantly during the experiment ($p < 0.5$). The left ventricular systolic pressure fell (mean fall 44 ± 11 mm Hg, $p < 0.01$) and left ventricular end diastolic pressure rose (mean rise $= 4 \pm 1$ mm Hg, $p < 0.02$) in all but one animal. Changes in right ventricular systolic and end diastolic pressures were not significant ($p < 0.8$ and $p < 0.3$ respectively).

Four animals were followed for 3 to 4 hours after the injection of contrast material. Left ventricular systolic pressure fell gradually until maximum volume was achieved at a mean time of 105 minutes and then rose gradually thereafter. During this period the pericardial sac was seen to expand and then to empty. In 3 animals after the maximum hemodynamic effects had occurred and the fluid had been with-

drawn and measured the fluid was re-injected and an additional amount of normal saline was added to produce cardiac tamponade. This required 60 to 85 ml of normal saline and the final fluid volumes were similar to those required in the study of Morgan and associates¹⁹ (100 to 300 ml of normal saline).

Discussion

Extravasation of contrast material into the myocardium or pericardial sac during selective angiography has been considered to be one of the serious potential complications of this technique.² Table III shows the incidence of extravasation of contrast material into the myocardium and pericardial space after angiography as reported by several authors.^{1,2,4,11,20} In a case reported by Eicher and associates thoracotomy was performed for the relief of tamponade. It is of interest that an active bleeding site into the pericardial sac was not demonstrated at operation. In our patient cardiac tamponade developed after the injection of contrast material into the left ventricle and was treated successfully with pericardiocentesis alone. The hematocrit of the pericardial fluid was only 5 per cent indicating the presence of 25 ml of blood (hematocrit of 40 per cent) in the pericardial sac which contained approximately 225 ml of fluid. If one estimates that 40 ml of the contrast material extravasated into the pericardial space along with 25 ml of blood and was added to 10 to 15 ml of pericardial fluid that was present

initially, the final volume estimated is 300 per cent greater than the initial volume. In our animal study, the mean volume injected was 16 ml and the mean final volume was 85 ml indicating a dilution of 550 per cent by solute free water from the pericardium and the epicardial surfaces. Therefore it seems to be likely that the cause of the accumulation of fluid and the development of cardiac tamponade after cineangiography in our patient was not active bleeding but the effect of the hypertonic solution. Further evidence for this hypothesis is the absence of the recurrence of pericardial tamponade or effusion after removal of the pericardial fluid in our patient as well as in the case reported by Pocock and associates.²¹

Although none of the dogs in our experiment developed cardiac tamponade, all had significant hemodynamic alterations. In 3 animals the addition of 60 to 85 ml of normal saline produced tamponade. However, these animals had normal hearts and pericardia. On the other hand, some patients with rheumatic heart disease are known to have extensive pericardial fibrosis and adhesions which may be sufficient to obliterate the entire pericardial space.²² Pericardial disease not only may decrease the distensibility of the pericardium but also may delay the absorption of contrast material from the pericardial space. Furthermore, cardiac enlargement may reduce the already limited distensibility of a diseased pericardium. Finally, although in our experiment radiopaque material was injected directly into the

Table III The incidence of extravasation of contrast material during cardiography

Author	Number of cases	Myocardial staining	Contrast used was in the pericardial sac without tamponade	Cardiac tamponade
Amplatz et al	280			1
Byrck et al	137			
	(147 L.V. punctures)	3	1	
Hillis and Herdip	250	1		1
Aker et al	102	2		
Bagger et al	2958	4		
Lehman et al	60			
	(7 tests)	7	1	

pericardial sac the transmucocardial extravasation of contrast material may reduce the ability of the heart to withstand tamponade.

Harris and co workers¹ have studied the effect of radiopaque materials injected into isolated closed intestinal loops of dogs. They demonstrated a marked augmentation of the volume of fluid in these loops and a decrease in the osmolality of the fluid. The same authors showed a decrease in plasma volume after the intragastric injection of contrast medium, suggesting that this transudate originated at least in part from the vascular space. Lehan and co workers²⁰ after injecting 4 ml of contrast material into the coronary arteries of dogs observed a massive transfer of myocardial tissue water to the capillaries as demonstrated by a fall of 30 to 50 per cent in coronary sinus hemoglobin, hematocrit and serum protein. The same authors have shown that the injection of a similar amount of radiopaque material into the iliac vein of the experimental animal produced a fall of only 5 per cent in hematocrit and a fall of 2 per cent in the hemoglobin concentration of the inferior vena caval blood. This indicates the importance of the role of the capillary bed in the resultant hemodilution. The intravascular injection of contrast material in man has been noted to cause an increase in plasma volume² and plasma osmolality.^{21, 22} It is evident that these agents because of their hypertonicity exert a powerful osmotic force on capillaries increasing capillary permeability.² The capillary wall acts as a semipermeable membrane and allows passage of fluid to neutralize the osmotic gradient exerted by these materials. It is our belief that these reports and the results of the present study explain the cause of the accumulation of fluid in the pericardial sac after the extravasation of radiopaque medium.

The diagnosis of extravasation of contrast material during cineangiography usually presents no problem because the operator will immediately notice the presence of radiopaque material in the pericardial sac. Once the diagnosis is established the patient should be followed closely and therefore if intra-arterial and venous catheters are in place they

should not be removed. The electrocardiogram and arterial and venous pressures should be monitored and the amount of pericardial fluid estimated by intermittent fluoroscopy. Since our patient developed cardiac tamponade within 70 minutes and the experimental data indicate that the longest period required to achieve the maximum expansion of the pericardial space was 167 minutes the patient should be followed in the catheterization laboratory for 2 to 3 hours. If cardiac tamponade does not occur within this period of time and the patient's condition is otherwise satisfactory the catheters may be withdrawn and the patient returned to his room for close observation. If cardiac tamponade supervenes pericardiocentesis should be performed immediately. Fluoroscopic guidance is helpful since the pericardial space is well outlined by the contrast material. Our patient as well as the patient whose case was reported by Pocock and co workers¹ was treated successfully with pericardiocentesis and the reaccumulation of fluid did not occur. Therefore it would appear that this procedure is the method of choice for initial emergency management. If the hematocrit of the fluid withdrawn is less than 10 per cent and the patient's condition is stabilized thoriotomy should be delayed because bleeding as the primary cause of tamponade is unlikely.

Summary

A 58 year old woman with rheumatic heart disease underwent cardiac catheterization. Left ventricular cineangiography resulted in the transmucocardial extravasation of contrast material into the pericardial space. Cardiac tamponade occurred 70 minutes later. One hundred eighteen milliliters of bloody fluid with a hematocrit of 5 per cent was removed by pericardiocentesis and the patient responded without further treatment.

In order to explain the mechanism of cardiac tamponade in the absence of significant bleeding 85 per cent Hypaque was injected directly into the pericardial sac of 8 dogs. In all animals the left ventricular systolic pressure fell. End diastolic pressure rose in 7 of 8 preparations. Mean pericardial fluid contents were augmented

by 550 per cent. This augmentation was directly proportional to the amount of the injectate but unrelated to the time interval necessary for the maximum effect to occur.

It is concluded that tamponade which follows the transmyocardial extravasation of contrast material into the pericardial space need not necessarily result from hemorrhage but may be due to the powerful osmotic force placed on capillary walls by this hypertonic solution. The initial treatment of these patients by pericardiocentesis is suggested. Thoracotomy should be reserved for those patients in whom the withdrawn fluid has a high hematocrit.

We are pleased to acknowledge the technical assistance of Mrs. Bess Jenkins and Mrs. Marguerite T. Brown and to thank Miss Christine Berlano for the preparation of the manuscript.

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The electrocardiogram in a case of hemiparalysis of the diaphragm in a newborn infant

Jerome R Dorkin MD*

Jerry Eklrick MD**

Camden N J

Unilateral paralysis of the diaphragm although a rare pediatric problem has been discussed in the literature many times since it was first described by Naunyn in 1902. The last comprehensive report was that of Ruler¹ in 1962. When associated with Erb's palsy, the prognosis is poorer but the diagnosis is more easily arrived at. However Blattner² and Schiffrin³ have published cases of isolated hemiparalysis of the diaphragm. In these cases the diagnosis is often missed or delayed. The present case is published because the diagnosis was suggested on the third day of life by the electrocardiographer before it was suspected clinically. In the literature concerning hemiparalysis of the diaphragm available to us there was no mention or description of electrocardiograms. The possibility that the electrocardiographic pattern observed in our case may be specific for the condition is therefore worthy of note.

Case report

The mother of the infant whose case is discussed in this report was a gravida iv para iii Negro woman admitted to the Cooper Hospital on March 7, 1965 in active labor. The prenatal course had been benign except for a slightly excessive gain in weight. After 6 hours of labor the membranes ruptured spontaneously. The fetal heart rate which had been regular at 140 per minute suddenly began to slow

became irregular and then could not be heard. Rapid delivery of a 9 pound female infant was effected by a mid forceps extraction over a right mediolateral episiotomy. The baby's 1 minute Apgar score was 5 and her cry was delayed for several minutes. Because of the low Apgar score, fetal distress and cyanosis she was admitted to the premature nursery.

On admission to the nursery the infant was cyanotic. The respiratory rate was 72 per minute with obvious distention of the abdomen. The lungs were poorly aerated and exhibited bilateral crepitations. The heart rate was regular at 120 per minute and no murmurs were heard. Femoral pulses were equal.

Placed in an incubator with 40 per cent oxygen the infant continued to exhibit respiratory distress, tachypnea and cyanosis. The report by one of us on an electrocardiogram recorded on March 10, 1965 (Figs 1 and 2) contained the following statement: "I wonder if there is not some odd anatomic abnormality, perhaps involving the diaphragm which results in extreme movements of the heart in various phases of respiration."

The chest x ray film then obtained exhibited some elevation of the right diaphragm (Fig 3) and on March 11, 1965 fluoroscopy revealed paradoxical excursions of the diaphragm thus a diagnosis of hemiparalysis of the right diaphragm was established. Bronchoscopy was negative.

Respiratory difficulty persisted for another 2 weeks with additional x ray films still showing the high right diaphragm. Several electrocardiograms continued to show the pattern displayed in Fig 1 but there seemed to be a gradual decrease in the degree of variability of the QRS complexes.

By April 6, 1965 symptoms of cyanosis and respiratory difficulty had abated and the infant was allowed to go home.

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Associate Card. Inset and Director of the Heart Lab. Cooper Hospital, Camden, N. J. Address: 2108 Federal

St. Camden, N. J.

**Pediatric Resident, Cooper Hospital, Camden, N. J.

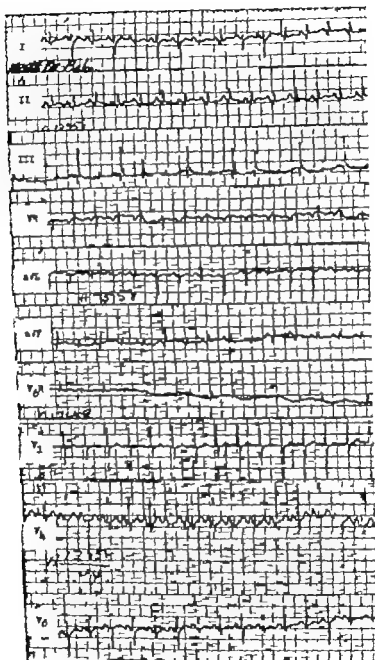


Fig. 1. Initial electrocardiogram recorded on March 10 1965.

On July 14 1965 a follow-up chest x-ray film (Fig. 4) showed a normal position of the right diaphragm. The last electrocardiogram (Fig. 5) no longer showed the unusual features noted on the original tracing.

Discussion

The interesting finding in this case and the reason for this report was the unusual

electrocardiogram. At first glance one gets the impression that some of the QRS complexes are premature but careful measurement indicates a regular rhythm. The P waves occur regularly and with no intrinsic variation. The possibility of aberrant ventricular conduction is ruled out by the fairly constant QRS duration and

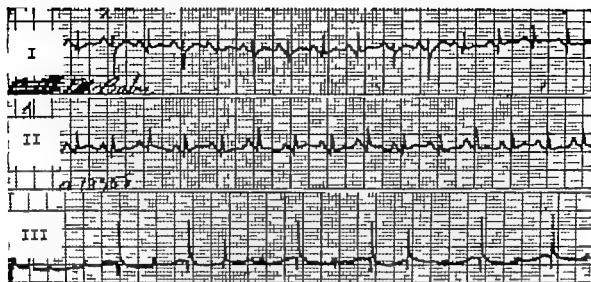


Fig 2 Enlargement of Leads I II and III shows in detail the unusual changes in QRS configuration. See text



Fig 3 Initial chest x-ray film shows the high right diaphragm



Fig 4 Follow-up chest x-ray film recorded on July 18, 1965, shows normal position of the diaphragm

the lack of any appreciable variation in T. Some QRS complexes consist of a q and a slurred R wave. Others display a qR_s and some are rS complexes. The greatest variability is seen in Leads I and III. If one first calculates the axis using the most negative complexes in Lead I and the most positive complexes in Lead III, and then calculates the axis represented by the most positive complexes in Lead I and the most negative in Lead III, one sees that it oscillates between +40 and

+134 degrees. The most plausible explanation for this phenomenon could be a swing of the heart about its anteroposterior axis from left to right. It was for this reason that the electrocardiographer suggested such a mechanism and x-ray examination and fluoroscopy tended to corroborate this impression. The movement of the thoracic contents with respiration was so marked and the mediastinum in the newborn infant was apparently so mobile that the heart was literally swinging about its

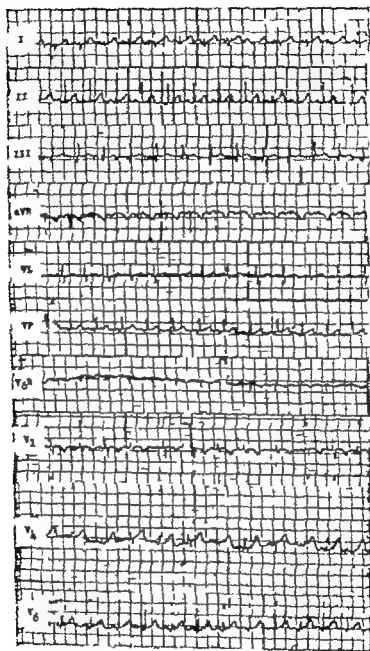


Fig 5 Follow-up electrocardiogram recorded on July 18, 1963. The tracing is now normal.

anteroposterior axis. At first thought it seemed to be impossible that the axis could swing from one extreme to the other within one or two cardiac cycles, but when one recalls that the respiratory rate was as high as 72 per minute and was typically rapid and jerky, the rate of change of the axis is quite believable.

A consensus of those observing cases of

hemiparesis of the diaphragm indicates that fluoroscopic observation of the seesaw movement of the diaphragm is the best diagnostic point. This is Kuenbock's sign and is described in a reference by Light.⁸ This seesaw movement of the diaphragm is the mechanism that causes the swinging of the heart from side to side, resulting in the electrocardiographic pattern

seen in our case. Our interpretation was further corroborated by the gradual disappearance of the QRS variations as the diaphragm began to respond in a more normal manner. At the present time with normal position of the right diaphragm (Fig. 4) the electrocardiogram no longer shows any variation of QRS from beat to beat (Fig. 5).

A more complete discussion of the clinical and pathologic findings in this disorder is beyond the purview of this report. For an excellent review and bibliography the reader is referred to the aforementioned report by Riley.¹ Other interesting case reports available to us were those of Tyson and Bowman,⁴ Blattner,² Light,³ Turner and Balst,⁶ Schiffrin,⁵ Bingham,⁷ and France.⁸

Summary

An unusual electrocardiographic finding which may be specific for cases of hemiparalysis of the diaphragm in newborn infants is presented.

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Congenital complete heart block in children

Charles R. Ayers MD

John P. Boineau MD *

Madison S. Spack MD **

Durham NC

Advances in the field of pediatric heart disease have included an improved evaluation of congenital complete heart block. Although associated cardiac malformations must be excluded there has been increased awareness that this condition probably occurs most frequently as an isolated entity.

Most physicians who care for children with this condition currently believe that those who have no associated heart defects usually do quite well; however reports in the literature indicate deaths related to this condition. This is a review of the historical aspects of this subject with a presentation of electrophysiologic and hemodynamic factors influencing the findings in this condition. Also a review of complications which have been reported is presented in an attempt to suggest optimal management for this group of children.

A Electrophysiology of heart block

Congenital heart block is the result of a disturbance in the propagation of excitation from the atria to the ventricles due either to an anatomic or purely electrical discontinuity in the specialized conduction pathways which ordinarily connect these two chambers. The studies of Robb and

Petri¹ and Paes de Carvalho and associates² have demonstrated localized tracts of specialized conduction tissue connecting S A and A V nodes. It is not known whether selective ablation of these preferential pathways produces A V block. The normal appearing QRS configuration in cases of congenital A V block indicates a relatively normal sequence of ventricular excitation due to a pacemaker located above the bifurcation of His. Wallace³ has observed that in the dog a pacemaker can be located above the bundle of His after heart block has been surgically produced.

Recent electrophysiologic studies by Hoffman⁴ and Paes de Carvalho⁵ on the mechanism of atrioventricular impulse transmission indicate that A V block may result from changes in the electrical characteristics of the cells in the A V node. These observations are especially significant in view of the possible mechanism of block in patients with the arrhythmia of congenital advanced but not complete A V block.

In the presence of a physically intact conduction pathway between atrium and ventricle advanced degrees of A V block are attributed to prolongation of the recovery period of excitable cardiac tissue

From the Department of Pediatrics, Duke University Medical Center, Durham, N.C.

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*Special Postdoctoral Fellow, National Heart Institute, United States Public Health Service.

**Address: Department of Pediatrics, Cardiology, Duke University Medical Center, Durham, N.C. 27704.

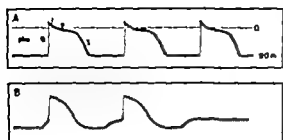


Fig. 1 Transmembrane action potentials of ventricular and A-V nodal fibers. *A* The refractory period of ventricular myocardium. The five phases (0 through 4) of an action potential of a ventricular fiber are illustrated to demonstrate the relationship between the recovery of excitability and the refractory period. From the beginning of excitation (Phase 0) through Phase 2 the fiber is refractory to the arrival of a premature impulse. Impulses occurring during the latter part of Phase 3 and during Phase 4 normally result in excitation of the fiber. *B* Refractoriness of A-V nodal tissue due to decremental conduction. The principle of refractoriness of specialized A-V node fibers to impulse propagation is shown by decremental conduction. The consecutive bursts shown illustrate the characteristic initial slow rise (foot) of nodal fibers of the N region of the A-V node. Note the progressive lengthening of the initial foot (decremental conduction) and failure to reach the necessary threshold for impulse propagation in the third burst.

Fig. 1A diagrammatically illustrates the four phases of an action potential from a ventricular fiber of the dog. A natural impulse arriving between Phase 0 and Phase 3 is not likely to excite cells at this stage of recovery and therefore will not be transmitted to more distal tissues. The absolute refractory period of excitable tissue corresponds to Phase 2 and part of Phase 3. The latter part of Phase 3 corresponds to the relative refractory period; excitation and propagation are more likely to occur when a stimulus is received at this stage. Phase 4 corresponds to the resting potential of the polarized cell and the tissue is readily depolarized during this period.

Although the relative and absolute refractoriness of myocardial tissue is meaningful in terms of a naturally generated impulse, the distinction is somewhat arbitrary under experimental conditions. Excitation has been found to depend on the strength and duration of an applied stimulus during the various phases.⁶

The term *refractoriness* is applied to the

mechanism of delayed or blocked impulse transmission through the A-V node region is of a different order. Pires de Carvalho⁴ has demonstrated different electrical properties of cells located in three regions of the A-V node—the atrionodal (AN) nodal (N) and nodal His (NH) regions. He as well as Hoffman⁴ have noted that both normal and abnormal delay or block in impulse transmission is localized to the N region. They have demonstrated that progressive delay with characteristic Wenckebach cycles can be produced with repetitive premature stimulation, acetylcholine and anoxia. The transmembrane potential curve of these cells has a distinctive initial slow rise (foot) from which the action potential occurs. With rapid atrial stimulation or exposure to acetylcholine delay in excitation occurs with progressive lengthening of the foot. Failure of propagation results when the initial rise fails to reach a critical threshold (Fig. 1B).

It is probable that a critical density of current is necessary for impulse propagation. If transmission is progressively slow or decremental this threshold is not attained. This mechanism is referred to as *decremental conduction*⁴ and can be used to explain advanced and possibly complete A-V block if an insufficient number of cells are simultaneously excited because of partial interruption of the pathway.

Atrioventricular dissociation is a useful electrocardiographic term to describe independent control of atrial and ventricular excitation by separate pacemakers. Three mechanisms of A-V dissociation that may operate singly or in combination in a given patient are the following: (1) Complete or incomplete physical discontinuity in the pathways of A-V conduction resulting in complete A-V dissociation due to complete forward block (e.g., congenital complete heart block with absence of the A-V node). (2) Electrical discontinuity due to abnormal properties of cells of the N region of the A-V node resulting in A-V dissociation and second degree advanced and possibly even complete A-V block due to varying degrees of decremental concealed conduction (e.g., second degree heart block with Wenckebach cycles). (3) Normal interference of impulse transmission due to (a) the collision of excitation waves from two

pacemaker sites one located above and the other in or below the A V node prior to the His bifurcation (b) normal block in the A V node producing failure to transmit some of the impulses arriving from rapid repetitive stimuli with the expected decrement in the V region and (c) concealed A V conduction with peripheral block because of failure to excite Purkinje or myocardial tissue due to the arrival of the impulse during an absolute refractory period of these tissues

Atrioventricular block in patients with rapid atrial rates as occurs in atrial flutter with a 2:1 block is an example of mechanism 3b. Atrioventricular dissociation in which the sinus pacemaker occasionally captures the ventricle principally involves mechanisms 3a and c. However for the dissociation to persist retrograde block

(mechanism 2 in reverse) must be implicated to explain the absence of atrial capture by the ventricle when the rate of the atria is slower than that of the ventricles. Similarly, some degree of forward block must be present in A V dissociation when the rate of the atrium is faster than that of the ventricle and only infrequent ventricular captures by atrial pacemaker are observed. Because of this fundamental relationship between A V block and A V dissociation a dynamic approach is essential in the evaluation of an individual clinical arrhythmia. The electrocardiogram in Fig. 2B illustrates a case of presumed congenital advanced A V block. The basic mechanism appears to be second-degree A V block with a typical Wenckebach period involving P_1 , P_2 and P_3 (P_4 is blocked). However P_4 should have been conducted

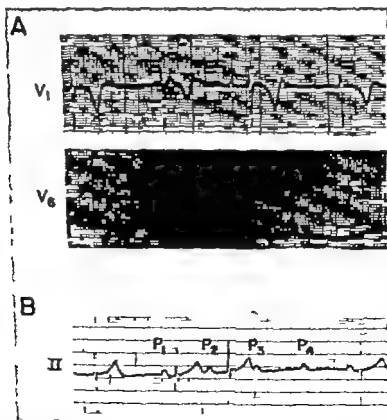


Fig. 2 Typical and atypical electrocardiograms in children with heart block. A. Complete atrio-ventricular dissociation due to complete A V block. Note that there is no relationship between the P waves and QRS complexes which are of normal duration. B. Complex arrhythmia demonstrating advanced A V block in a 7 year-old child. The mechanism of this arrhythmia is discussed in the text.

lost consciousness and became moribund. Immediate application of an external pacemaker at a stimulation rate of 120 per minute produced a dramatic change. Within 1 minute the child regained consciousness and with continued pacing he became quite alert and showed marked diminution in respiratory rate after 5 minutes. While pacing was continued cardiac catheterization was promptly carried out with documentation of a patent ductus which was surgically corrected. Thereafter the child became asymptomatic.

Review of the literature suggests that the prognosis in congenital heart block is related primarily to cardiac adaptation to stress and to the occurrence of Stokes-Adams attacks (which may be caused either by ventricular asystole or ventricular tachycardia and fibrillation). The newborn period presents an especially vulnerable time for these patients. Reports of mortality occurring in the newborn period suggest^{21,22} that such infants with heart rates of less than 50 beats per minute are especially likely to succumb. Later in infancy, the occurrence of febrile illnesses may also produce a hazardous situation.^{23,24} The mechanisms of poor adaptation of the newborn and infant to stressful situations remains to be clarified, however superimposed metabolic acidosis leading to further slowing of heart rate may be an important factor. In these situations intermittent external pacemaker therapy may be lifesaving.

Elucidation of the incidence of Stokes-Adams attacks in children with congenital complete heart block is difficult although such episodes are considered to be infrequent. However evidence is strong that patients with congenital complete heart block with a widened QRS complex (idioventricular pacemaker²⁵) are especially prone to such episodes.^{26,27} In these patients with broad QRS complexes one is faced with the question of whether permanent pacemaker implantation is indicated. The high incidence of death in this particular group suggests strong consideration of this method of therapy if Stokes-Adams episodes develop. Also in any child with complete heart block who has had two or more Stokes-Adams attacks permanent pacemaker therapy should be strongly

considered as suggested by Nakamura and Nadas.¹

Molthan and associates²⁸ reported on thirty-five children with congenital complete heart block and of these three died with Stokes-Adams attacks (all of these had electrocardiographic evidence of a widened QRS complex). Nakamura and Nadas reported on sixty-one children of whom thirty had associated congenital cardiac defects suspected clinically or documented at catheterization. In their series one death occurred in a child shown to have no cardiac defects and an additional twelve who had associated heart disease died during childhood. The mechanism of death in their patients was primarily sudden onset of severe congestive heart failure.

In our own experience we have followed twenty children with congenital complete heart block in the past 6 years. Of these five have had evidence suggestive of associated heart disease and have undergone cardiac catheterization. Of those catheterized two had no associated defects, one had a secundum atrial septal defect and two had patent ductus arteriosus. Those with congenital defects underwent surgical correction. Two years postoperatively the child with the secundum atrial defect whose QRS was of normal duration died suddenly at home. By history the episode was a characteristic Stokes-Adams attack. Thus one patient of the total group of twenty developed Stokes-Adams syndrome and died.

The question remains as to the optimal management of the asymptomatic child with congenital complete heart block who has no evidence of associated congenital heart disease. Although periodic checkups are indicated these patients should be managed as normally as possible. The physician caring for this group of children is in a dilemma when asked what the ultimate fate of such children will be in adult life. This important information can only be available after large series of children with congenital heart block have been followed into adult life.

Summary

Although absolute evidence of the congenital nature of the heart block rests upon

the diagnosis being made before or immediately after birth children shown to have complete heart block at a later age who have a QRS complex of normal duration and who have a negative history for inflammatory diseases which might cause heart block should be considered and managed as though they had congenital complete heart block. The prognosis in this condition is largely related to cardiac adaptation to stress and to the occurrence of Stokes Adams attacks. Increased stress leading to severe congestive heart failure is most likely to occur during the newborn period and during febrile illnesses in infancy. All associated cardiac malformations place the patient in a vulnerable position with the possibility of the onset of rapid heart failure. Stokes Adams attacks are most likely to occur in those children who have widened QRS complexes electrocardiographically. Although it is difficult to clarify the true instance of Stokes Adams attacks in children who have complete heart block with a supraventricular pacemaker such episodes are unusual. During episodes of increased stress in which heart failure is likely to occur intermittent external pacemaker therapy may prove to be lifesaving. The difficult problem of therapy for repeated Stokes Adams attacks should be approached with consideration of permanent pacemaker therapy.

Those patients without symptoms and/or associated heart disease generally do well and should be managed as normally as possible with intermittent checkups. In view of the absence of reports concerning the ultimate fate of a large series of children with documented congenital heart block, valuable information would be provided by a long term cooperative investigation between cardiology groups caring for children and adults to elucidate the course of such children as they proceed into adult life.

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Fundamentals of clinical cardiology

The clinical significance of true left axis deviation

Left intraventricular blocks

Ray Pryor MD*

S Gilbert Blomst Jr MD**

Denver Colo

With rare exception true left axis deviation is an abnormal electrocardiographic finding. This communication will deal with the pathophysiology, causes and clinical significance of left axis deviation in acquired and congenital heart disease. Left inferior intraventricular blocks will be briefly compared with left superior intraventricular blocks.

Definition of terms

True left axis deviation (LAD)—Deviation of the mean QRS axis (\bar{AQRS}) to the left and superior of 330 degrees (-30 degrees) i.e. between 270 (-90) and 330 degrees in the frontal plane (Fig 1).

Mean QRS vector (\bar{AQRS})—The average of all instantaneous vectors during the QRS interval.

Initial QRS vector—The average of all instantaneous vectors during the first 0.04 second of the QRS interval.

Terminal QRS vector—The average of all instantaneous vectors during the last 0.04 second of the QRS interval.

Anatomy of left ventricular conduction system

A brief review of the conduction system of the left ventricle is pertinent and will

make the discussion of peripheral left intraventricular conduction defects more logical.

At the tip of the interventricular septum the common bundle bifurcates into a right and left bundle branch. Shortly after the left bundle appears on the left side of the interventricular septum it divides into two groups of fibers. One group fans out as a radiation of fibers that spreads superiorly and anteriorly over the subendocardium of the anterolateral wall; this group is called the superior (anterior) division of the left bundle. The second group also fans out but radiates inferiorly and posteriorly toward the inferior surface of the left ventricle; it is called the inferior (posterior) division of the left bundle. Fig 2 illustrates these divisions or radiations viewed through the left ventricle. Many investigators^{1,2} have observed these two major divisions of the left bundle whereas others^{3,4} reported that the left bundle appeared to fan out over the endocardial surface of the left ventricle but discrete separate divisions were not described. It is important to at least conceptualize the fibers of the left bundle as being arranged into superior and inferior divisions in order to rationally approach

*In the Division of Cardiology Department of Medicine, University of Colorado Medical Center, Denver, Colorado.
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**Chief, Professor of Medicine, Director of Cardiology, University of Colorado Medical Center, 4200 East
Ninth Avenue, Denver, Colorado 80202.

**Professor of Medicine, Head, Division of Cardiology.

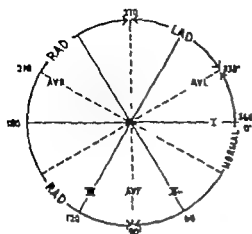


Fig. 1 The frontal plane reference figure demonstrating the boundaries of LAD RAD and normal QRS

the diseases that alter the sequence of depolarization of the myocardium supplied by these divisions. These two divisions of the left bundle freely anastomose peripherally in the subendocardial layers of the ventricle via a network of Purkinje fibers.

Electropathophysiology of left intraventricular blocks, including post-infarction blocks

Normally excitation spreads simultaneously along both divisions of the left

bundle. If a lesion should involve a sufficiently large number of fibers of one division the sequence of excitation would be altered. If the lesion should dominantly involve the superior division fibers excitation would spread down the inferior fibers, travel through Purkinje anastomoses and finally spread superiorly; the QRS loop would be counterclockwise, the terminal QRS vector would point leftward and superiorly, and LAD would occur. As long as the conduction system was used throughout excitation there would be little or no QRS prolongation, but if the lesion was extensive or so situated as to force excitation out into the slowly conducting myocardium QRS prolongation would occur because of a broad terminal vector (slowing of the terminal forces of the loop). If the lesion involving the superior division is fibrosis, the initial QRS vector will be inferior and leftward (normal), the terminal vector superior and leftward, and LAD will be the result (Fig. 3A). This type of conduction defect may be called *left superior intraventricular block* (SIVB) or *primal block* of the superior division of the left bundle; the former being preferable. If the lesion is necrosis (infarction) the direction of the terminal vector and QRS will be similar to that for the previous conduction defect, but the initial vector will be directed

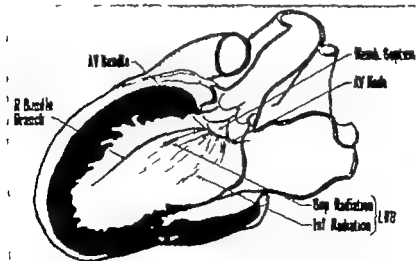


Fig. 2 Drawing of the superior and inferior radiations of the left bundle, viewed through the left ventricle (Courtesy of Dr. Robert I. Hawley, Denver, Colorado)

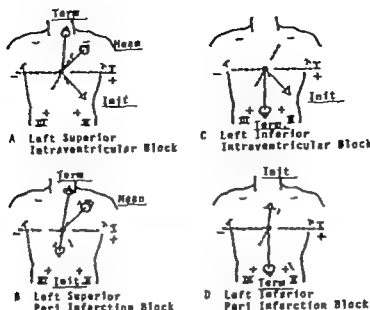


Fig 3 A Drawing of the vectors for superior intraventricular block (SIVB) B Superior peri infarction block (SPIB) C Inferior intraventricular block (IIVB) D Inferior peri infarction block (IPIB)

inferiorly and rightward (abnormal) away from the infarcted area in the superior or anterior lateral wall (Fig 3B). This type of conduction defect may be called *left superior peri infarction block* (SPIB) or *postinfarction block*. The word *superior* is used instead of *anterolateral* in order to maintain continuity of terminology with the anatomy of the conduction system and with the other location of intraventricular blocks.

Experimental work with laboratory animals supports the concept that lesions involving the superior division may cause the terminal QRS forces to shift leftward and superiorly. In separate experimental studies Uhly and Rivkin¹⁴ and Watt and Pruitt¹⁵ observed this leftward and superior rotation of QRS forces after laceration of the superior (anterior) radiation of the left bundle in dogs. In another study Watt, Murao and Pruitt¹⁶ found an even greater leftward and superior shift of the mean electrical axis in the frontal plane (sufficient to satisfy criteria for clinically significant left axis deviation in human beings) after laceration of the anterior ramus of the left bundle branch in the baboon (primate) heart as compared to the canine heart study.¹⁴

Although the remainder of this paper will deal with causes and clinical significance of LAD at this point it is appropriate to briefly discuss and illustrate the counterpart of superior intraventricular blocks namely left inferior intraventricular blocks.

Should there be a necrotic lesion in the inferior wall involving the fibers of the inferior division of the left bundle the initial QRS vector would point leftward and superiorly away from the inferior infarct. Excitation of the inferior wall would be clockwise and the terminal vector would point inferiorly (90 degrees). This type of intraventricular conduction defect may be termed *left inferior peri infarction block* (IPIB) or *postinfarction block* (Fig 3D). Inferior peri infarction block is illustrated in Fig 4 but will not be discussed further in this paper.

LAD due to superior peri infarction block (necrosis) or superior intraventricular block (fibrosis)^{1-3, 17, 18} and inferior peri infarction block (necrosis)^{1-3, 17, 18} are well described and largely accepted as electrocardiographic entities. Why not *left inferior intraventricular block* (IIVB) or *parietal block* of the inferior division

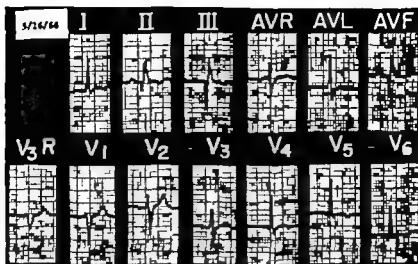


Fig. 4 Fifty-one year-old man with ECG illustrating inferior infarction and inferior post infarction block (IPIB)

of the left bundle due to fibrosis only without necrosis? This entity was recently suggested¹² but has otherwise been undescribed probably because the electrocardiogram would appear to be normal. We believe that inferior intraventricular block may be a recognizable electrocardiographic entity and will herewith be described and compared with superior intraventricular block.

If fibrosis in the left ventricle involves predominantly the distribution of the inferior division of the left bundle the sequence of excitation may be altered in a fashion opposite to that of SIVB. Excitation would spread initially through the superior division and then travel inferiorly giving a clockwise loop and a rather inferior (90 degree) terminal QRS vector (Fig. 3 C). In both superior and inferior intraventricular block the initial 0.04 second vector is directed inferiorly and leftward (normal). However the very early QRS forces e.g. the 0.02 second vector direction may be slightly different when the two types of block are compared. In SIVB excitation starts down the inferior division thus the 0.02 second vector may be more inferior accounting for the small 0.03 second r wave in Leads II, III and aVF and the small 0.02 second q wave in Lead aVL. Conversely in IIVB initiation of excitation through the superior division usually causes the 0.02 second

vector to be oriented a bit more superiorly causing a small initial 0.02 second r wave in Lead aVL and small 0.02 second q waves in Leads II, III and aVF. The terminal QRS vector points toward the blocked (by fibrosis) radiation in each type of intraventricular block. SIVB is easily recognized by the finding of LAD (1b normal) with a normal initial 0.04 second vector.

How may we postulate that IIVB be recognized? It is apparent that the previously described initial vector terminal vector and QRS loop in IIVB outlines a normal electrocardiogram—but normal for whom? As people get older the terminal QRS vector tends to become directed more and more horizontally leftward but not superiorly enough to cause LAD. On the basis of the foregoing discussion it is logical to predict that IIVB will be manifested by an unusually inferior terminal QRS vector in a patient who should not have this direction of terminal forces i.e. a patient more than 45 years old with a medium to heavy body build especially if left ventricular enlargement is coexistent. An inferior terminal QRS vector is normal in young people and in older people who are tall or slender. Right ventricular enlargement must be clinically excluded as the potential cause of the inferior terminal vector. The initial and terminal vectors for IIVB due to only fibrosis are depicted

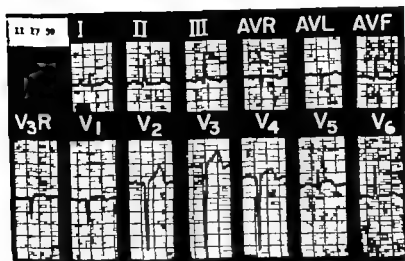


Fig 5 Fifty five year-old man ECG shows a terolateral infarction left ventricular enlargement (LVE) and an unusually inferior terminal QRS vector for age and LVE thus possible inferior intra-ventricular block (IIVB) is suggested. Autopsy revealed anterior infarction, no inferior infarction, left ventricular enlargement and no right ventricular enlargement. Fibrosis in the inferior division of the left bundle was found on histologic study (Courtesy of Dr Robert L. Hansley, Denver, Colorado).

in Fig 3 C. Experimental work suggests that IIVB should be real rather than hypothetical. Uhley and Ravkin¹ and Watt and Pruntt¹⁴ found that the terminal QRS forces shifted inferiorly after ligation of fibers of the inferior division of the left bundle. We have collected many clinical cases of IIVB and in the majority of these the patients were found to have ischemic heart disease, hypertension or diabetes and many had left ventricular enlargement. We have found only 2 cases of IIVB that have come to autopsy and had careful histologic examination of the proper areas of the myocardium for lesions. The electrocardiogram in Fig 5 was taken on a 55 year old patient with a medium body build and clinical ischemic heart disease. Recent anterior infarction and left ventricular enlargement are apparent. The terminal QRS vector is unusually inferiorly directed for age, body build and left ventricular enlargement. Clinically, right ventricular enlargement was not present. Thus, this electrocardiogram was believed to be suggestive of IIVB (partial block of the inferior division of the left bundle). The initial QRS vector is somewhat superior but the q waves in Leads II and III are not broad enough to be read as indicating inferior infarction.

Admittedly, the frontal plane vectors could be due to old inferior infarction with inferior per infarction block and partial normalization (narrowing of previously 0.04 second Q waves) of the initial vector. Gross postmortem examination revealed left ventricular enlargement, no right ventricular enlargement, recent anterior infarction and no inferior infarction. Careful histologic examination showed significant fibrosis involving the inferior division of the left bundle.¹⁵ The other autopsied case of clinical IIVB also revealed fibrosis involving the inferior division. More work needs to be done in this area, especially with carefully planned clinical pathologic correlative studies.

Causes and clinical significance of left axis deviation

Superior intraventricular block (SIVB)
Reports stating the incidence (0.2 to 1.2 per cent) of LAD found in electrocardiograms taken on healthy asymptomatic adults¹⁶⁻¹⁸ and the occurrence (0 to 1.4 per cent) of LAD in normal children^{19,20} confirm the view that LAD is rarely a normal electrocardiographic finding. Hiss, Lamb and Allen²¹ showed only a 0.8 per cent incidence of true LAD in their study of 6737 asymptomatic sub-

jects and most of the patients with LAD were more than 40 years old.

It has been shown that LAD is not related to the position of the heart in the chest or to body build.²⁹ Aging alone is not a significant factor in LAD.²⁹

Originally, LAD tracings without perinfarction block were called pure bundle block tracings but later Crant³⁰ suggested that pure bundle and perinfarction block were members of a family of ventricu-

lar conduction defects which as a group should be called left intraventricular blocks. We like this term but have added the word *superior* to fit the anatomy and to separate SIVB from the previously postulated IIVB.

The most common cause of LAD is SIVB due to fibrosis caused by ischemic heart disease. Several clinical and electrocardiographic pathologic correlative studies^{2, 12, 19, 20} show a high degree of corre-

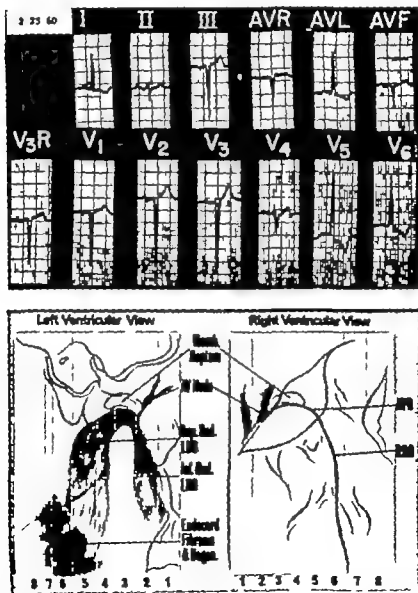


Fig. 6. ECG from a 55-year-old man illustrates LAD and superior intraventricular block (SIVB). Autopsy revealed LAD. B. During histologic study a fibrotic lesion involving the superior radiation of the left bundle was found. (Courtesy of Dr. Robert I. Hawley, Denver, Colorado.)

lation between LAD and clinical cardiovascular disease or left ventricular lesions (fibrosis, necrosis or myocardiopathy). In our own study²⁸ we collected 302 new cases of LAD over a 5 year period. Clinical correlation revealed that more than 80 per cent of the patients had ischemic heart disease, hypertensive cardiovascular disease, diabetes, obesity, or aortic valve disease. SIVB was the reading in 84 per cent of the electrocardiograms. Twenty-eight of the patients with SIVB came to postmortem examination and 27 had coronary artery disease. Twenty-four of these 27 patients were found to have fibrosis only, whereas the other 3 had old myocardial infarctions. Two of these 3

patients with infarction showed old antero-lateral infarction on the electrocardiogram without fulfilling the criteria for superior per infarction block (SPIB). No abnormality of the heart was described in 1 autopsied patient with LAD. In a separate double blind electrocardiographic pathologic correlative study²⁹ all of 8 autopsied patients with LAD were found to have lesions of the superior radiation with SIVB correlating with fibrosis and SPIB correlating with necrosis each time. The electrocardiogram (ECG) shown in Fig. 6A was taken on one of the patients in this study. Left atrial enlargement (LAE) and left ventricular enlargement (LVE) with ST-T changes are seen. The

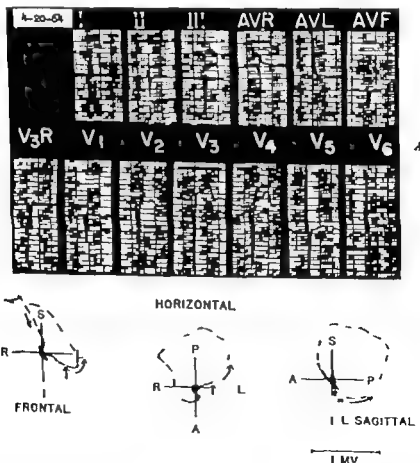


Fig. 7 Fifty-year-old male. A ECG demonstrates LVE, LAD, SIVB and old anterior infarction. B VCC (Frank lead system) confirms the anterior infarction since the 00-second vector is posterior to the 0-180-deg (R-L) line; the horizontal plane. Note normal initial forces, counterclockwise loop, superior terminal forces and LAD in the frontal plane.

initial QRS vector is leftward and inferior (normal) the terminal vector is leftward and superior resulting in LAD due to SIVB. Postmortem examination revealed coronary artery disease and a fibrotic lesion involving the superior radiation was found by the pathologist during serial histologic studies of the conduction system. The lesion is depicted in Fig. 6B.

The ECG in Fig. 7A shows LVE and LAD due to SIVB. But is the poor r wave progression in Leads V_1 , V_2 due only to LVE or is there an associated old anterior infarct? The vectorcardiogram (VCG) has proved to be very helpful in the recognition of anterior infarction in patients with LVE.¹⁰ In the horizontal plane the 0.02 second vector is anterior to the 0.180 degree line with LVE alone but is posterior to that line with anterior infarction. The VCG in Fig. 7B is compatible with anterior infarction. Of course the ECG could represent SPIB with normalized initial forces in the frontal plane but since the criteria for SPIB are not met the ECG is read as indicating LVE, LAD, SIVB, old anterior infarction and ischemia.

LAD may be present in patients with marked LVE especially when due to aortic incompetence; however the LAD is not due to the LVE alone but suggests fibrosis in addition.

Left bundle branch block (LBBB) is an interventricular conduction defect manifested by a leftward shift of the very early QRS forces from a control ECG. QRS broadening, secondary ST-T changes, a narrow QRS loop and a normal leftward axis in the frontal plane. If an ECG with LBBB shows LAD, additional superior intraventricular block is suggested. The ECG shown in Fig. 8A illustrates LBBB, LAD and SIVB. The tracing in Fig. 8B was taken on the same patient 2 years and 7 months later when the LBBB was not present. The early initial forces have shifted rightward (new small q in Lead aVL and r in Lead III) which proves that the previous ECG indicated LBBB. LAD is still present suggesting that LAD with LBBB does mean SIVB also. The ECG with LBBB and LAD in Fig. 8C was taken on a patient who died with sarcoid heart disease. Postmortem examination revealed extensive lesions involving both the proxi-

mal main left bundle and the peripheral superior division thus providing pathologic correlation with the LBBB and the LAD.¹¹

Right bundle branch block (RBBB) is an interventricular conduction defect characterized by QRS broadening and a broad slurred terminal blocked right bundle vector that is directed rightward and anteriorly causing the broad terminal S in Lead I and R in Lead V_1 . With RBBB the sequence of left ventricular excitation is not altered therefore the unblocked (before the RBBB comes in) initial mean and terminal vectors should be normal. If there is LAD of the unblocked mean (first 0.06 to 0.08 second of QRS interval) vector it carries the same connotation as LAD without RBBB. The ECG in Fig. 9A shows LAD due to SIVB. The ECG in Fig. 9B was taken on the same patient 9 years later. RBBB has occurred but the unblocked QRS forces still show LAD, thus SIVB can be read in the presence of RBBB.

LAD has been reported in diseases that involve the myocardium primarily or secondarily, e.g. LAD was found in 64 per cent of patients with *obscure cardiomyopathy*¹² in 50 per cent of subjects with *cryptogenic cardiomyopathy*¹³ in 19 of 35 patients with *idiopathic myocardial hypertrophy*¹⁴ and in 7 of 9 patients with *scleroderma*.¹⁵ Sixteen of our 51 patients with *cardiac amyloidosis* had LAD.¹⁶ LAD has also been reported in *myotonia atrophica*, *progressive muscular dystrophy*, *Friedreich's ataxia*, *myocarditis*, *familial cardiomyopathy*, *hemochromatosis* and *alcoholic cardiomyopathy*.¹⁷

The type of ECG changes if any caused by fibrosis, amyloid, etc. may depend on the relative degree of involvement of certain areas of the myocardium and on the amount of coverage given to these areas by the superior and inferior divisions of the left bundle. In some hearts histologic study reveals that the superior radiation is more dominant in distribution. If the lesion predominantly involved the area of the fibers of the superior division SIVB might occur. If involvement of the inferior division predominated inferior intraventricular block might be seen on the ECG. If the disease process in the

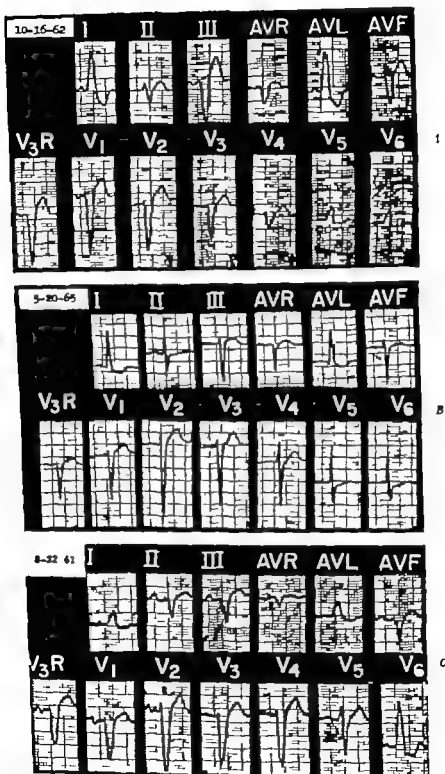


Fig. 3. A. Sixty-three year-old woman whose ECG shows left bundle branch block (LBBB) and LAD suggest-
ing SIVB. ECG taken 2½ years later (B) does not show LBBB but LAD and SIVB persist. C. ECG from a
55-year-old man with sarcoid heart disease illustrates LBBB, LAD, and SIVB. (step 7) and sarcoid lesions
involving both the main left bundle and the fibers of the superior division.

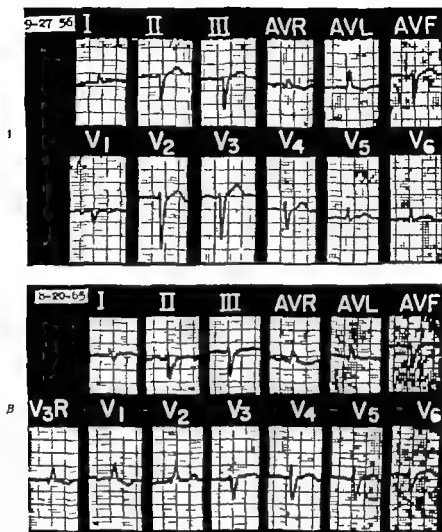


Fig 9 Forty-year-old man. *A* ECG demonstrates LAD and SIB. *B* ECG 9 years later reveals right bundle branch block (RBBB) but LAD of the unblocked QRS forces and SIB can still be read in the presence of RBBB.

myocardium was diffuse and widespread some degree of electrical neutralization of forces might cause the terminal vectors to be directed normally and thus there would be no recognizable intraventricular block. Occasionally extensive diffuse involvement of the heart with amyloid has caused the initial and terminal forces to point away from the left ventricle (i.e. at 210 degrees).

Hyperkalemia is a potential cause of LAD that has not been previously reported. We have seen several patients who had hyperkalemia and LAD that disappeared after dialysis and a return of the serum potassium to normal levels.

The ECG in Fig. 10 *A* was taken when the patient's serum potassium was 8.0 mEq per liter. The tall T waves and QRS broadening (the initial and terminal forces participate in the widening) of hyperkalemia are apparent and LAD is present. After dialysis when the serum potassium was normal the ECG in Fig. 10 *B* was recorded and is observed to be normal without LAD. The pathogenesis of LAD with hyperkalemia is not known at this time. The answer will probably be found in myocardial cellular metabolism.

Surgical injury of the superior division of the left bundle is a cause of LAD. Transient LAD occurred in one of our patients

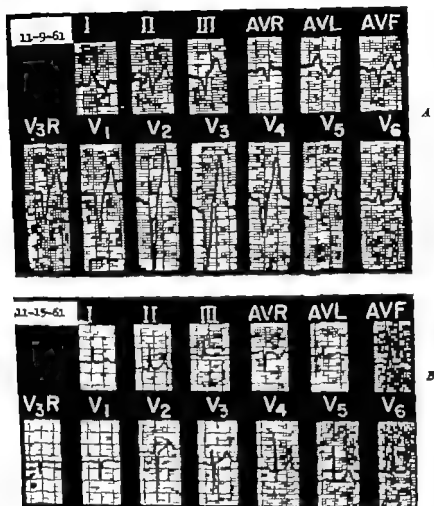


Fig 10 4 Fifty-eight year-old woman with hyperkalemia (serum potas mm = 8 mEq/L) ECG is compatible with hyperkalemia and LAD noted B After dialysis the serum potas mm and the ECG returned to normal

immediately after aortral valvulotomy with a transventricular dilator LAD has been reported to occur after transventricular aortic commissurotomy. After surgery for both congenital discrete fibrous sub-aortic stenosis and idiopathic hypertrophic muscular subaortic stenosis (IHSS) several of our patients have developed LAD with a marked leftward and superior shift of the terminal QRS vector. This suggests that a proximal lesion or damage to the superior division early in its course in the interventricular septum is capable of causing LAD and SIVB. The ECG in Fig 11A is a preoperative control tracing from a patient with IHSS demonstrating LAD, LVE and ST-T changes. At operation a relatively large amount of hypertrophic

left septal muscular tissue was removed. Immediately after operation the ECG showed LBBB and LAD (Fig 11B) suggesting surgical damage to both the left bundle and to its superior division. Seven months after operation (Fig 11C) the LBBB had disappeared but the LAD was still present compatible with permanent surgically induced SIVB. The development of LAD after operation for the above mentioned two types of sub-aortic stenosis in 4 different patients is comparable with the experimental animal studies quoted earlier.¹¹

Pulmonary emphysema has been said to be a cause of LAD. Most patients with parenchymal lung disease and varying degrees of right ventricular enlargement

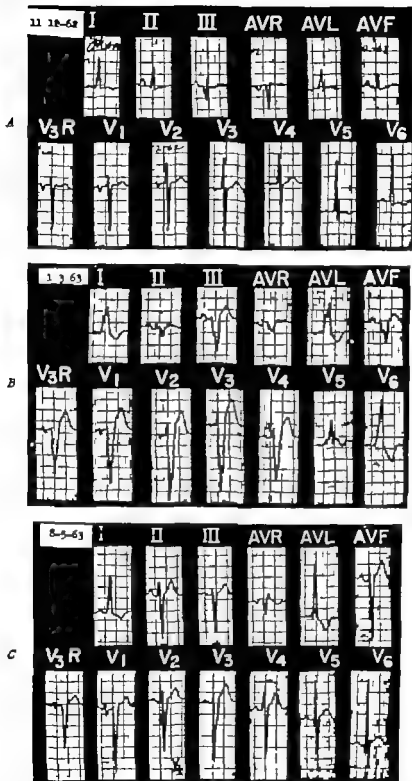


Fig 11 A Twenty three year-old man with idiopathic hypertrophic subaortic stenosis (IHSS). ECG shows left atrial enlargement (LAF) and LVH. B After removal of a moderate amount of hypertrophic left septal tissue LBBB and LAD developed because of surgical injury of the left bundle and its superior division. C Seven months after operation the LBBB had disappeared but persistent LAD suggests permanent damage to the superior division.

(RVE) will show in the frontal plane a rightward terminal QRS vector with right axis deviation and a clockwise loop or $S_1S_2S_3$ pattern (normal leftward inferior initial vector rightward superior terminal QRS vector and an unplottable $\bar{A}QRS$ because of rotation of the loop through the electrical center of the heart in traveling toward the right shoulder terminally). In patients with emphysema the terminal QRS vector may be rightward and superior in the frontal plane but not uncommonly the loop rotates counterclockwise causing the ECG to resemble that of LAD. For this type of ECG of emphysema we prefer the term *pseudo-LAD* since the ECG of emphysema is usually easily recognized and thus distinguished from that of left ventricular conduction

defects. Grant³ suggested that the abnormal conductance of the emphysematous lungs deforms the electrical field surrounding the heart which might explain the unusual loops in some of these patients. The pseudo-LAD of emphysema (usually due to RVE) may be distinguished from the true LAD of left SIVB by the following characteristics. The P vector is relatively inferior causing an inverted P wave in Lead aVL, a flat P in Lead I and prominent P waves in Leads II, III, and aVF. The QRS voltage is usually low in the limb and precordial leads. The terminal QRS vector is very superior but usually somewhat rightward causing a small terminal s wave in Lead I and a terminal R wave in Lead aVR that equals or exceeds the terminal R wave in Lead aVL.

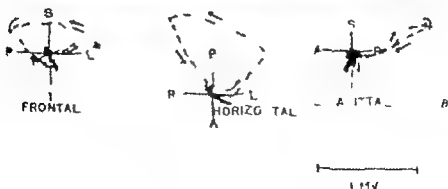
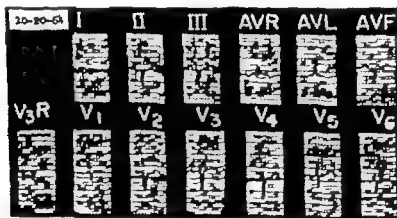


Fig. 1. A Fifty-eight year-old man with emphysema. Note the inferior P vector, low QRS voltage, and superior rightward terminal QRS vector with counterclockwise loop. Lead aVR resembles Lead aVL. ECG illustrates the pseudo-LAD of emphysema. B Frank lead system VCG shows the superior rightward terminal QRS vector with counterclockwise loop in the frontal plane—probably represents right ventricular enlargement with the electrical field influenced by the emphysematous lungs.

The P wave QRS and T wave are often very similar in Leads aVR and aVL . In SIVB the terminal QRS vector is leftward and superior with good magnitude. The terminal R wave in Lead aVL is relatively tall and significantly exceeds the terminal r (if present) in Lead aVR . No terminal s wave in Lead I is seen with SIVB and the P wave is rarely inverted in Lead aVL . The ECG in Fig. 12A is a typical example of pseudo-LAD that may be seen with emphysema. The terminal QRS vector is superior and rightward with a counter-clockwise loop. The VCG (Frank lead system) in Fig. 12B shows this loop in the frontal plane. In the horizontal plane the terminal portion of the loop is posterior and relatively rightward. The ECG and VCG are compatible with RVE and pseudo-LAD in a patient with emphysema. If the ECG of a patient with emphysema really resembles that of true LAD and SIVB additional ischemic heart disease should be considered.

Superior periinfarction block (SPIB)
The term periinfarction block was suggested by W. T. McCallum, MD University of Oklahoma School of Medicine and introduced by First Bayley and Bedford.⁴ These authors' diagnostic criteria of periinfarction block included (1) evidence of myocardial infarction of the subendocardial region of the ventricular wall or transmural infarction with a circumferential region of subendocardial damage (2) QRS complexes in the limb leads which are or exceed 0.11 second in duration (3) a characteristic QRS pattern in the unipolar precordial and extremity leads. Grant and associates^{5,6,7} amplified the concept of periinfarction with different and more definitive criteria which are (1) an abnormality of the direction of the initial forces of the QRS interval of a type characteristic of myocardial infarction (accounting for Q waves) (2) an abnormality of the direction of the last forces of the QRS interval so that they come to point opposite to the initial QRS forces and (3) little or no prolongation of the QRS interval.⁸ On the basis of the anatomy of the left ventricle and its conduction system Grant provided very logical explanations for the left intraventricular conduction defects. These im-

portant fundamentals have already been discussed in the *Electropathophysiology* section of this paper. Some authors (Burchell¹⁴ Pruitt¹⁵ Castle⁷) prefer the term post-infarction block rather than periinfarction block. Periinfarction block is the senior member of the left intraventricular block family and for many years has been such a helpful and faithful friend that we are inclined to stick by it. More importantly we will check our premises. If we adhere to precise rules recognize the limitations and place periinfarction block in its proper clinical perspective it should continue to serve as a valuable electrocardiographic entity. The rules limitations and clinical importance of superior periinfarction (SPIB) will now be discussed.

Grant⁶ raised the question whether a patient with infarction might develop changes in the terminal forces without deformity of the initial forces (no Q waves). At that time he had collected 10 cases of periinfarction with normally directed initial 0.04 second vectors and autopsy proof of infarction but a recent preinfarct control ECG was available in none of the cases. We have not seen any cases of periinfarction block that never had an abnormal initial 0.04 second vector but we have seen several patients with old infarction proved clinically by previous ECG and/or autopsy who had normal initial forces at some later time. In an ECG with LAD this might occur with (1) normalization of initial forces with time (2) electrical neutralization of initial forces by another differently located infarct and (3) leftward and superior shift of the entire electrical field.⁶ If an isolated ECG shows LAD with normal initial forces SIVB is the best reading for without control or previous electrocardiograms there is no way of knowing whether the above mentioned possibilities have been in action or whether infarction or only fibrosis will be found at autopsy. Recent studies^{12,16} suggest that if autopsy fibrosis is the common denominator in cases of LAD and that the abnormal initial 0.04 second vector direction of infarction should be required before the term SPIB is used. Even then there are limitations for the ECG in patients with

rather marked LVE (especially with aortic valve disease) may resemble that of SPIB and only fibrosis may be found at autopsy. In our study ²⁴ 14 per cent of 302 new cases of LAD in a 5 year period met the criteria for SPIB. Twelve of these patients with SPIB came to autopsy. All 12 were found to have coronary artery disease and fibrosis. A myocardial infarct was found in 9 of the 12 hearts and the other 3 showed rather marked LVE.

We recommend that Grant's original

criteria for SPIB be used as follows: (1) true LAD (2) an abnormal rightward inferior initial R04 second QRS vector in the frontal plane (3) abnormal leftward superior terminal QRS forces in the frontal plane (4) either normal or prolonged QRS duration due to slowing of the terminal forces. An r' in Lead V_1 or broad slowed terminal QRS forces favor SPIB. Control electrocardiograms and clinical confirmation (history, enzyme rises, etc.) are desirable in the presence of rather

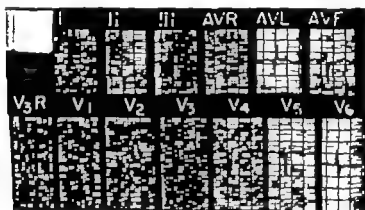


Fig 13 Seventy nine year-old man. ECG demonstrates rightward inferior initial QRS vector, leftward superior terminal vector with Lead V_1 and LAD—anterolateral superior infarction with superior peri infarct too big (SPIB) and no broadening of QRS.

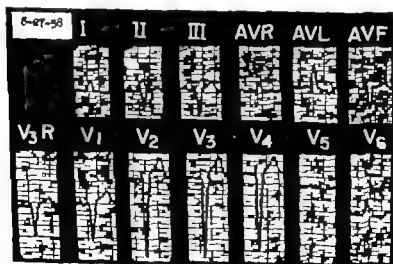


Fig 14 Eighty seven year-old man with acromegaly. ECG shows LVE, LAD and QRS widening due to broadened terminal forces not decreased r_s in Lead V_1 with M shaped complex—superior peri infarction block with QRS broadening. Autopsy revealed an old anterolateral infarction.

marked LVE or cardiomyopathies conservative terminology e.g. SIVB is often warranted. Even if the angle between the initial and terminal QRS vectors exceeds 110 degrees with LAD, SIVB is probably the wisest terminology if the initial 0.04 second vector is normally directed.

SPIB commonly occurs with anterolateral and superior infarctions and less commonly with strictly anterior locations. Some patients with pre-existing LAD and SIVB may later have an infarction but when there is no control ECG the cause of the LAD (SIB versus SIVB) may not be determined.

The ECG in Fig. 13 is an example of SPIB with a normal QRS duration; the r in Lead V_1 is commonly seen with SIB but rarely in SIVB.

The ECG in Fig. 14 was recorded on an 86 year old man with acromegaly and LVE clinically. The ECG is an example of SPIB with QRS widening and falsely resembles LBBB. The q in Lead aVL and the r in Lead III are not quite diagnostically broad but the decrease in r in Lead V_1 and the W shaped QRS complex in Lead V_1 along with the LAD suggest that this is SPIB and not LBBB. The QRS complexes are more likely to be broad and bizarre when LVE and SPIB coexist. Autopsy revealed LVE and old anterolateral infarction. SPIB has been especially helpful in providing the proper diagnosis and logical explanation for the ECG with LAD and QRS broadening that looked like LBBB. LBBB alone does not cause LAD divergent initial

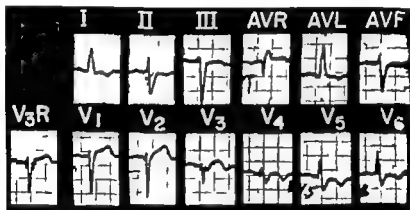


Fig. 15 Sixty year-old man ECG illustrates anterior infarction LAD small q in Lead aVL and QRS widening due to broad, slow terminal forces—superior pex infarction block is read as the cause of the LAD because of the terminal slowing of the loop.

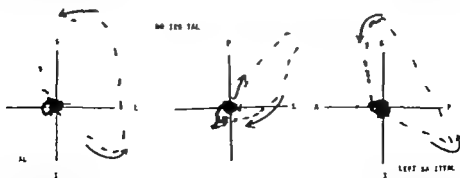


Fig. 16 Same patient as in Fig. 15. Frank lead system VCG demonstrates the terminal slowing of the loop manifested by an increased number of dots bunched together. In the frontal plane LAD with counterclockwise loop is noted. In the horizontal plane the clockwise loop is characteristic of a anterolateral infarction.

and terminal vectors or slowing of only terminal forces. Part and even recent articles in the literature contain numerous examples of electrocardiograms read as indicating LBBB and infarction that were actually good examples of SPIB without LBBB.

In Fig 15 the ECG shows anterior infarction LAD and QRS broadening due to slowing of the terminal forces. In spite of the normally directed initial vector in the frontal plane SPIB is likely because

of slowing of the terminal forces. The VCG in Fig 16 on the same patient shows this terminal slowing manifested by an increased number of dots bunched together. The clockwise loop in the horizontal plane is characteristic of anterolateral infarction.

The ECG in Fig 17 A is an example of acute anterolateral superior infarction with LAD SPIB QRS broadening and r in Lead V₁. The ECG taken 2 years later on the patient is shown in Fig 17 B and

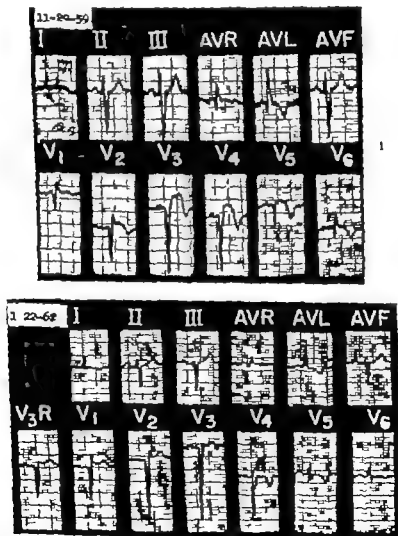


Fig 17 A Fifty-five-year-old man ECG shows acute anterolateral superior infarction with superior peri infarction block and some QRS widening. Note r in Leads V₁. B ECG recorded a little over 2 years later illustrates normal rotation of the initial vector in the frontal plane. LAD and r in Leads V₁ are still present. The anterior component of the old infarct can be seen in Leads V₃ and V₄.

tivity. Although inhibition of this enzyme system is well established, enzyme activity is affected by changing electrolyte concentration so that changes in the distribution of sodium and potassium by digitalis induced interference with a carrier system might secondarily inhibit the enzyme. The fact that digitalis apparently interferes with the flux of substances that are not actively transported such as chloride and of organic molecules such as glucose might support this latter interpretation. So would the observation that potassium cannot only obliterate the toxic manifestations of digitalis but can also restore normal activity of membrane ATPase. Electrophysiologic studies of the effect of digitalis on the cell membrane are compatible with either hypothesis. The demonstration that low doses of digitalis appear to stimulate the enzyme and actually increase the influx of potassium strongly favors a direct effect on the enzyme rather than a mechanism involving competition for carrier sites.

Two studies utilizing coronary A-V differences have noted that a loss of potassium from the heart is consistently associated with the increased contractility produced by digitalis. Furthermore one study indicated that the increase in contractility was proportional to the loss of potassium. An analogy has been made with the so called staircase effect in which rapid stimulation of the heart produces progressively more forceful contraction. As with digitalis this rapid stimulation is associated with progressive loss of potassium from the muscle presumably due to a reduction in the time available in diastole for re entry of potassium.

Despite these observations there is much to suggest that the increased force of contraction produced by digitalis is not related to a loss of potassium. There are several experiments in which animals whose heart failure had been compensated by digitalis were then sacrificed. They showed no decrease and sometimes even an increase in potassium as compared to the potassium-depleted state associated with congestive heart failure itself. Moreover studies of potassium flux and potassium concentration in isolated tissues have produced variable results depending on the tissue and technique used. There are many re-

ports that show no change in the concentration or flux of isotopically labeled potassium in ordinary ventricular muscle at therapeutic rather than toxic doses of digitalis.

Others report that the effect of digitalis in increasing contractility can be demonstrated before any change in potassium flux or indeed any electrophysiologic evidence of digitalis effect on ventricular muscle can be documented. Significant effect on the concentration of potassium in skeletal muscle can be demonstrated without any significant change in the force of contraction. Finally the studies which most strongly suggest a close relationship between loss of potassium and contractility have employed coronary A-V differences a technique affected by a number of variables and not so reliable as some of the techniques which have failed to show this correlation.

Effects on intracellular calcium. Because of a growing consensus that the inotropic action of digitalis cannot be attributed to its effect on potassium metabolism there has been a search for other possible intracellular changes produced by digitalis that might account for this action. It has long been known that an increased concentration of calcium like digitalis has a positive inotropic effect and that the concentration of calcium has at least a permissive role on digitalis induced increased contractility. There are several reports of either an increase in intracellular calcium or an increase in calcium flux at therapeutic doses of digitalis. There are also studies that fail to confirm this. As of this writing it would appear from the literature reviewed that there is probably a small pool of labile calcium whose flux rate is increased by therapeutic doses of digitalis. Just how this increased lability of calcium affects contractility is uncertain but certain reasonable possibilities exist. The immediate mechanism for cardiac contraction is the sliding and perhaps folding of actin molecules along the myosin molecules resulting in shortening of the sarcomere. The energy for this is supplied by ATP which releases its high energy phosphate. The influence of myosin A.T.P. is the latter myosin molecule. I actin also

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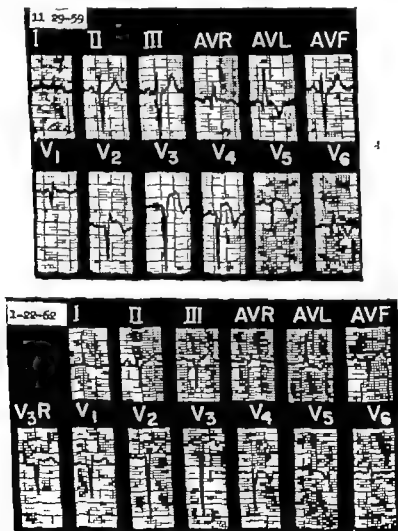


Fig. 17. A. Eight year-old man. ECG shows acute anterolateral-superior infarction with a infarction block and some QRS widening. Note r in Leads V₁. B. ECG recorded a little over illustrates normalization of the initial vector in the frontal plane LAD and in Leads V₃₋₆. The anterior component of the old infarct can be seen in Leads V₁ & V₂.

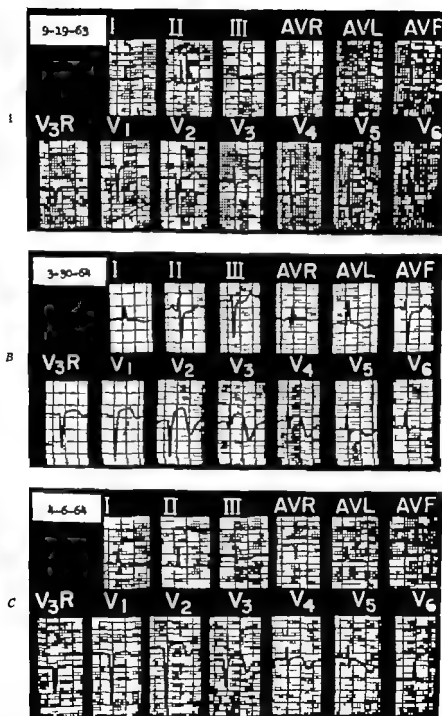


Fig. 18 Forty nine year-old woman. *A* Normal control ECG. *B* ECG shows acute anterior infarction with LAD and superior peri infarction block. *C* One week later ECG shows disappearance of LAD and S1 IB. See text for explanation.

some interesting changes are noted. The QRS interval has narrowed to a normal duration and the initial QRS vector in the frontal plane has normalized. The initial vector in the horizontal plane is still diagnostic of infarction but if the initial vector had also normalized in the V leads, or if only the limb leads were available the etiology of the LAD (SIV versus SPIB) would not be known although the r' in Lead V_1 would favor SPIB. The presence of LAD in such a case is helpful for it at least points to left ventricular disease.

SPIB may occasionally be transient or paroxysmal. Fig 18A shows a control ECG. The ECG taken on the same patient at the onset of infarction shows acute anterior infarction with LAD and SPIB (Fig 18B). One week later the ECG (Fig 18C) still showed anterior infarction but no LAD. Observe the small q in Lead aVL in Fig 18B and its disappearance in Fig 18C. This sequence suggests that the infarct blocked conduction through the superior division and forced early initial excitation down the inferior division giving a slightly more inferior initial vector on March 30 1964 (Fig 18B). The disappearance of the q in Lead aVL and the LAD on April 6 1964 (Fig 18C) indicates that the infarct no longer blocked conduc-

tion through the superior division and thus allowed simultaneous excitation down both divisions resulting in initial and terminal forces in the frontal plane similar to those of the control ECG in Fig 18A. Infarction (anterior or anterolateral) is capable of blocking the superior division proximally near its origin. This may be one of the reasons why some authors object to the term per infarction block (block causing conduction to go around infarction).

Congenital heart disease. In the acyanotic patient with congenital heart disease, *endocardial cushion defects* are the most common cause of LAD occurring in more than 80 per cent of these patients.⁴ The LAD in cases of endocardial cushion defect is not due to LVE but is thought to be due to a congenital abnormality of the conduction system. Studies of the conduction system in cases of this lesion have shown abnormalities with displacement of the A-V node and A-V bundle.^{24,47} Fig 19 illustrates a typical ECG of endocardial cushion defect with LAD and right ventricular enlargement.

LAD is seen in slightly more than 15 per cent of all cases of isolated *ventricular septal defects* and it is believed that these defects which cause LAD are of the endocardial cushion type. Abnormalities of the

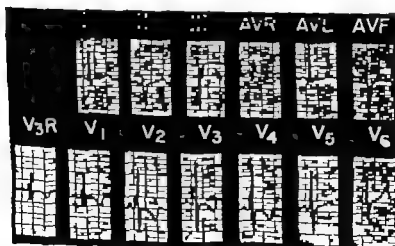


Fig 19 Twelve-lead ECG of a boy with an endocardial cushion defect. ECG demonstrates LAD and right ventricular enlargement (RVL). Note the notch on the S wave in Leads II, III and aVF—probably the onset of the absence of right ventricular enlargement on the electrical field. This notch is commonly seen with right ventricular

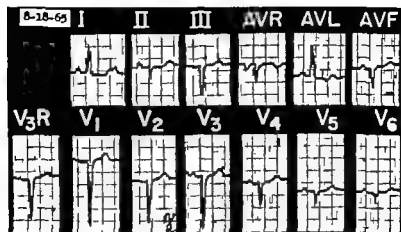


Fig. 20 Twelve-lead ECG of 12-year-old boy with corrected transposition and no other associated defects. ECG shows LAD and rhythm strip recorded runs of 2:1 A-V block.

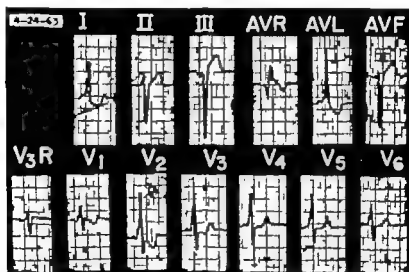


Fig. 21 Twenty-two-year-old woman with Fallot's tetralogy. ECG demonstrates LAD due to the pre-excitation syndrome (type B) which masks the expected RAD and RVI with tetralogy.

conduction system in cases of this lesion have also been demonstrated.^{12,43}

LAD has occurred not uncommonly in corrected transposition with left-sided apex especially in patients with no other associated cardiac defects except frequent A-V block (2:1 or complete).⁴⁴ With inversion of the ventricles and the conduction system⁴⁵ unusual electrical fields would not be unexpected in these patients. An ECG showing LAD (Fig. 20) and runs of 2:1 A-V block were recorded on a 12-year-old boy with corrected transposition and no

other associated defects proved by cardiac catheterization and angiography.

The pre-excitation syndrome (type B) is an occasional cause of LAD. The ECG in Fig. 21 was recorded on a 22-year-old woman with Fallot's tetralogy and the pre-excitation syndrome with LAD. The expected right axis deviation and right ventricular enlargement are masked by the anomalous conduction.

In the cyanotic group tricuspid atresia is the major lesion that causes LAD. In a cyanotic patient if the ECG shows right

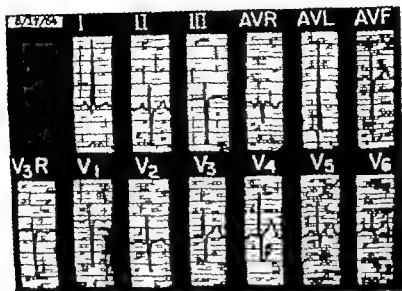


Fig 27 7-year-old boy with tricuspid atresia ECG illustrates LAD LVE and LAD

atrial enlargement (especially with small foramen ovale) left atrial enlargement no right ventricular enlargement but left ventricular enlargement and LAD in tricuspid atresia will be the diagnosis with rare exception. The ECG in Fig. 22 recorded on a 6-year-old child with tricuspid atresia, demonstrates left atrial enlargement LVE (35 mm R in Lead aVL) and LAD.

Slightly over 30 per cent of patients with single ventricle will have LAD. Some patients with large complete endocardial cushion defects (AV communis) will be cyanotic.

LAD has been observed in some very rare forms of congenital heart disease such as isolated right ventricular hypoplasia.¹ In cor triloculare right axis deviation is usually present but 2 cases with LAD have been seen.²⁴

Summary

The anatomy of the left ventricular conduction system and the electrophysiologic of left intraventricular blocks have been presented. Inferior intraventricular blocks have been compared with superior intraventricular blocks.

A new electrocardiographic entity named left inferior intraventricular block (LIVB) or parietal block of the inferior division

of the left bundle is herein postulated and described.

With rare exception true left axis deviation (LAD) is an abnormal electrocardiographic finding. The most common cause of LAD is superior intraventricular block (SIVB) or parietal block of the superior division of the left bundle due to fibrosis caused by ischemic heart disease. Other possible causes of LAD with SIVB are obscure cardiomyopathies idiopathic myocardial hypertrophy scleroderma cardiac amyloidosis myotonia atrophica progressive muscular dystrophy Friedrich's ataxia myocarditis familial cardiomyopathy hemochromatosis and alcoholic cardiomyopathy.

LAD in the presence of LBBB or RBBB suggests a more peripheral SIVB in addition to the proximal interventricular block.

Superior parainfarction block (postinfarction block) is a senior member of the left intraventricular block family and an important cause of LAD although it probably occurs somewhat less frequently than was previously thought.

Hyperkalemia is presented as a new reversible cause of LAD.

Surgical injury to the superior division of the left bundle may cause LAD after operation for congenital discrete fibrosis

subaortic stenosis or idiopathic hypertrophic muscular subaortic stenosis

The pseudo LAD seen with pulmonary emphysema has been described

In cyanotic patients with congenital heart disease LAD is very common with endocardial cushion defects and occurs in slightly more than 15 per cent of all cases of isolated ventricular septal defects LAD may be seen in cases of corrected transposition with left sided apex especially in patients without other associated defects The pre excitation syndrome (type B) may cause LAD

In cyanotic patients with congenital heart disease tricuspid atresia is the major lesion that causes LAD LAD is present in slightly more than 30 per cent of patients with single ventricle Rare forms of cyanotic congenital heart disease that may cause LAD are isolated right ventricular hypoplasia and cor biloculare

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Others report that the effect of digitalis in increasing contractility can be demonstrated before any change in potassium flux or indeed any electrophysiologic evidence of digitalis effect on ventricular muscle can be documented. Significant effect on the concentration of potassium in skeletal muscle can be demonstrated without any significant change in the force of contraction. Finally, the studies which most strongly suggest a close relationship between loss of potassium and contractility have employed coronary A-V differences, a technique affected by a number of variables and not so reliable as some of the techniques which have failed to show this correlation.

Effects on intracellular calcium. Because of a growing consensus that the inotropic action of digitalis cannot be attributed to its effect on potassium metabolism, there has been a search for other possible intracellular changes produced by digitalis that might account for this action. It has long been known that an increased concentration of calcium like digitalis has a positive inotropic effect and that the concentration of calcium has at least a permissive role on digitalis induced increased contractility. There are several reports of either an increase in intracellular calcium or an increase in calcium flux at therapeutic doses of digitalis; there are also studies that fail to confirm this. As of this writing, it would appear from the literature reviewed that there is probably a small pool of labile calcium whose flux rate is increased by therapeutic doses of digitalis. Just how this increased lability of calcium affects contractility is uncertain, but certain reasonable possibilities exist. The immediate mechanism for cardiac contraction is the sliding, and perhaps folding of actin molecules along the myosin molecules, resulting in shortening of the sarcomere. The energy for this is supplied by ATP which releases its high energy phosphate under the influence of myosin ATPase. The latter can be found on bridges between the actin and myosin molecules. These bridges also con-

tain calcium and magnesium—calcium favors contraction and magnesium depresses it. Since digitalis can be found in this approximate area of the cell it would seem that an action on myosin ATPase similar to its effect on membrane ATPase could well explain its effect. Unfortunately, no effect of digitalis on myosin ATPase can be demonstrated. On the contrary, there is suggestive evidence that rather than stimulating myosin ATPase directly, digitalis acts by interfering with physiologic inhibitors of contraction. A contaminant of artificial preparations of actomyosin was found to be necessary for relaxation of the muscle strip after each contraction. This substance called relaxing factor has been found to be a portion of the invagination of the cell membrane called sarcoplasmic reticulum that surrounds every myofibril. It has a very high affinity for calcium. In the polarized state the relaxing factor and the Z lines contain high concentrations of calcium. With depolarization some of the calcium shifts to actomyosin. Its shift back to the relaxing factor during repolarization permits relaxation. It has been hypothesized that digitalis reduces the affinity of these sites for calcium and thus facilitates mobilization of calcium to actomyosin at the time of depolarization. This change in affinity may be produced by the inhibition of an ATPase, but the evidence for this is not clear.

An interesting facet of the isotropic action of digitalis is that it is absolutely dependent on beat—the time of onset of increased contraction is inversely proportional to the heart rate. If cardiac tissue is incubated with digitalis for one half hour and then washed, there will be no increase in contractility. How this dependence on beat fits with the effect of digitalis on mobilization of intracellular calcium is yet to be explained.

Effects on cardiac electrophysiology. The electrophysiologic effects of digitalis on the other hand would appear to be closely linked to its effect on potassium flux. The direct effects of digitalis on membrane resistance, depolarization and repolarization can be well explained mathematically in terms of changes in potassium concentration and flux and the associated changes in sodium. Moreover, such electrolyte changes

have actually been documented at the time when these membrane changes occur. An apparent paradox exists in that some electrophysiologic changes can occur with low concentrations of digitalis. Yet as mentioned above, net loss of H^+ cannot ordinarily be demonstrated at full therapeutic levels. The explanation for this paradox lies in the differing sensitivity of different cardiac tissues to the potassium wasting effects of digitalis. When the sensitivity of the Purkinje fiber and that of the ventricular muscle were compared, marked changes occurred in the specialized conduction tissue before there was any effect on the ordinary myocardium. The data are less clear for the rest of the specialized conduction system but it is likely that a similar sensitivity is present.

Effects on other organs. The effects on the central nervous system are also mediated through a change in sodium and potassium pumping. It is likely that the digitalis effect on peripheral and cardiac nerves is mediated in the same way. Similarly, the known important direct effect of digitalis on the kidney is concerned with sodium and potassium transport.

The mechanism of other noncardiac actions of digitalis is more uncertain. Digitalis can interfere with the transport of glucose, lysine and other substances in the small bowel. It is uncertain whether these actions are coupled to the sodium-potassium pump or represent a direct effect of digitalis on a separate carrier system. Finally, there are no data on the cellular basis for the direct effect of digitalis on the peripheral vasculature.

All this suggests that digitalis has two separate effects on the intracellular milieu, both of which can be useful in heart disease. These effects would appear to be produced by interference with different enzymes or carriers. Such a dichotomous view of the action of digitalis is not completely satisfying, and it has been suggested by some that the two actions are interrelated—that changes in the flux of one electrolyte produces changes in the availability of carriers for other electrolytes. Thus, for instance, a primary action of the $Na^+ H^+$ pump which could be compensated for and be undetectable might lead to measurable changes in calcium lability. Inferential evidence [

Annotations

A comparison of the electrical ventricular fibrillation threshold with and without anesthesia

The recent advances in diagnostic therapeutic and in investigative cardiology have been possible in large part as a result of the increasing use of complex electronic equipment. However, the use of such equipment subjects the patient to the very real risk of electrically induced ventricular fibrillation.¹ Studies in this laboratory have emphasized that the danger of causing ventricular fibrillation exists when there is (1) a significant difference in the electrical potential between an electrical source and the heart and (2) when there is a low resistance path by which allows the delivery of a concentrated current directly to the heart.²⁻⁴ Such a low resistance path is possible when the heart is exposed by thoracotomy when electrode catheters or conventional catheters containing guide wires or needles are introduced into the heart when needles or delicate catheters are used for pericardiocentesis when electrode wires are used for pacing the heart and during bronchoscopy tracheal aspiration gastrotomy and similar procedures if the instruments used are conductors and come into close proximity to the heart.

It has been shown that 20 microamperes of 60-cycle per-second alternating current can produce ventricular fibrillation in an anesthetized dog with an electrode catheter in the right ventricle. The mean current required to produce ventricular fibrillation on 215 occasions in 20 dogs was 7.38 microamperes (range 20 to 800 microamperes). One hundred eighty microamperes of 60-cycle per-second alternating current produced ventricular fibrillation in a anesthetized human being during operation with the electrodes directly on the heart (mean for 4 patients 553 microamperes). It has been suggested that such low electrical ventricular fibrillation threshold might exist because of the effects of the anesthetic agent.⁵ In order to test the possible effects of anesthesia on the electrical ventricular fibrillation threshold measurements were made in the same animal before and after anesthesia.

A 56-pound mongrel dog was trained over a period of several weeks to remain calm and tolerate a catheter in the jugular vein. A 16 electrode catheter was passed to the right ventricle. A 25

square-centimeter stainless steel plate was sutured securely to the abdominal left chest near the sternum. Adequate 2 per cent promaine HCl insured freedom from pain at the catheter and suturing sites. Electrocardiographic electrodes were firmly applied to the four extremities. The dog was then placed in a supporting sling. Right ventricular pressure and the electrocardiogram were continuously monitored.

When the pressure and heart rates indicated that the animal was stable progressively larger alternating currents were passed through the electrode catheter-dog-steel plate circuit for 2-second intervals by the technique previously described. Starting with 50 microamperes the current was increased by 50 microamperes during successive 2-second periods of stimulation until ventricular fibrillation was induced. Ventricular fibrillation occurred in the unanesthetized dog with a current of 500 microamperes. The animal promptly lost consciousness and normal sinus rhythm was restored with an externally applied D.C. shock of 200 watt-second. The dog did not appear to suffer any ill effects from the production and cessation of the ventricular fibrillation. He continued to be calm and permitted a intraosseous injection of pentobarbital sodium (30 mg. per kilogram) for general anesthesia. After the right ventricular pressure and heart rate had been observed to again be stable for 10 minutes the procedure as described above was repeated on two successive occasions. The electrical ventricular fibrillation threshold observed on both occasions were the same as in the unanesthetized state 500 microamperes.

The results of this study in a single dog are significant in that they indicate that the electrical ventricular fibrillation threshold can be the same in both the unanesthetized and anesthetized animal. It cannot be assumed therefore that anesthesia lowers the threshold and makes the animal more susceptible to low levels of current. A repetition of this type of study in a single dog can be trained to accept a fibrillating current would hardly appear to be justified. Similar studies obviously cannot be carried out in man. That the threshold was the same on one occasion makes it inadvisable to assume that the electrical fibrillation threshold reported both for the anesthetized dog and human may be valid for the unanesthetized state in both dog and man.

The minimum alternating electrical current that

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Reprint requests to Dr. J. H. H. H. H.

has produced ventricular fibrillation in the dog 120 microamperes that in adult man at open heart surgery 180 microamperes. Whether infants and children have a lower threshold than the dog is unknown in view of the variability of biologic response and the potential gravity of ventricular fibrillation it would appear that any piece of power-line-operated equipment used in connection with patients in whom there is a low resistance pathway to the heart should never have a current leak of more than 10 microamperes.

Henry D McIntosh MD

Frank Starmer MD EE

Robert E Phillips MD

Cardiovascular Laboratory

Department of Medicine

Duke University Medical Center

Durham N C

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A study of the oral flora in children receiving sulfadiazine prophylaxis against rheumatic fever

Continuous chemoprophylaxis against streptococcal infection is recommended to prevent recurrences of rheumatic fever. Statistical studies have demonstrated no difference between the efficacy of orally administered sulfadiazine and penicillin. Penicillin prophylaxis has been shown to alter the oral flora,^{1,2} but comparable studies have not been made in regard to sulfadiazine. This study was designed to evaluate the effect of long term continuous sulfadiazine prophylaxis on the oral flora.

Twenty-one children from the Grady Memorial Hospital Cardiac Clinics who were receiving continuous sulfadiazine prophylaxis against rheumatic fever as recommended by the American Heart Association for a minimum of 6 months comprised the study group. These children varied in age from 5 to 13 years; there were 7 males and 14 females. No child had received penicillin or other antibiotic for at least 30 days prior to the study. Sulfadiazine had been administered to these children for an average duration of 7½ years with the duration of prophylaxis varying from 6 months to 6 years.

A control subject was chosen for each child in the study by taking the child of the same sex whose name appeared next on the roll in the patients' class at school; the control subject had received no antibiotic therapy for 30 days prior to the study.

Study of the oral flora was performed in the following manner:

1. Cultures for alpha streptococci, coagulase positive staphylococci, *Neisseria* (oral and lactobacilli). The material to be cultured was collected on a cotton

swab. The swab was placed in the right upper mucobuccal fold and swept across the mucosa of the cheek to the lower right mucobuccal fold area. It was then carried up the buccal gingiva across the lower right molar teeth and down the lingual gingiva into the floor of the mouth. Maintaining contact with the floor of the mouth the swab was carried to the left side of the floor of the mouth. It was then carried up the lingual gingiva across the molar teeth and into the lower left mucobuccal fold. The swab was swept across the mucosa of the left cheek into the upper fold area over the buccal gingiva, the molar teeth and to the palatal area. The child was then led to extend the tongue while the throat was swabbed with a counterclockwise motion starting and ending in the left tonsillar area. The swab was placed in BBL 01604 transport medium and taken to the laboratory for culture.

In the laboratory the swab was removed from the transport medium with a sterile hemostat and carefully washed in 2 ml of beef infusion broth. A 0.03 ml quantity was placed on both a blood agar plate and a tomato juice agar special and streaked with the tip of a glass rod. The blood agar plates were inoculated and examined after 48 hours. The tomato juice agar plates were examined after 4 days.

The examination of the blood agar plates consisted of (1) Gross inspection and gram staining of colonies suspected of yielding alpha streptococci, staphylococci, *Neisseria* and yeast. (2) Alpha streptococci were identified as those colonies showing zones of red blood cells immediately surrounding

the colony and composed of chains of gram positive cocci which were not bile soluble. Three colonies on each plate were checked for bile solubility. (3) If typical staphylococci were found coagulase tests were done. Only coagulase positive staphylococci were tabulated. (4) If gram negative diplococci resembling *Neisseria* were found an oxidase test was done directly on the blood agar plate.

The examination of the tomato juice agar plate consisted of (1) Gross inspection of the plate with a hand lens or wide field microscope for colonies typical of the lactobacilli group. (2) Gram staining of suspected colonies for gram positive diphtheroid like bacilli. No attempt was made to confirm them biochemically as lactobacillus.

Findings on the cultures were recorded as tabular form thus: no colonies, few to moderate number of colonies, profuse growth of colonies.

2. Smears for fastiform bacilli and spirilla. Material for the smear was collected with a sterile wire loop introduced into the gingival sulcus on the buccal aspect of the lower right first permanent molar and on the buccal aspect of the lower left first permanent molar. The material was diluted in a drop of water and smeared on slide.

The smear was stained with crystal violet and examined for fastiform bacilli and spirilla. If only occasional organisms were seen the slide was recorded as negative. If organisms were present in large numbers the slide was recorded as positive.

It should be understood that the biochemical tests used for identification of the bacteria are by no means definitive in the sense that biochemical and serologic studies give conclusive evidence of the identity of a bacterium. However it is thought that such presumptive evidence of identification does provide valuable information and final results are interpreted with full knowledge of the limitations imposed.

Table I Alpha streptococci

	Sulfadiazine	Control
No growth	0	0
Moderate growth	1	7
Profuse growth	20	13

ALPHA STREPTOCOCCI. The cultures for alpha streptococci were positive in all children in both groups. However cultures for 20 of the 21 children in the sulfadiazine group showed a profuse growth of the organism whereas only 14 of the 11 control cultures showed profuse growth. The difference between the two groups was significant at the 5 per cent level (see Table I).

CHARACTER POSITIVE STAPHYLOCOCCI. One child in the sulfadiazine group had a moderate growth of the organism in culture. The other children in both

groups had negative cultures for coagulase positive staphylococci.

NEISSERIA. All children in both the sulfadiazine and the control groups had positive cultures for *Neisseria* with no difference noted between the groups.

LACTOBACILLI. Cultures for lactobacilli showed no significant difference between the sulfadiazine and the control groups (see Table II).

Table II Lactobacilli

	Sulfadiazine	Control
No growth	12	11
Moderate growth		7
Profuse growth	2	3

YEAST. Yeast cell occurred in equivalent number in the sulfadiazine and in the control groups.

FASTIFORM BACILLI AND SPIRILLA. Smears for fastiform bacilli and spirilla were recorded only as positive or negative. There was no difference between the sulfadiazine and the control groups (see Table III).

Table III Fastiform bacilli and spirilla

	Sulfadiazine	Control
Positive	16	14
Negative	5	

A difference in the oral flora between the sulfadiazine and the control groups was noted with only one organism the alpha streptococcus. A significantly increased number of alpha streptococci was present in the oral flora in children receiving sulfadiazine prophylaxis. In the preliminary study the sensitivity of the alpha streptococci to sulfadiazine and other chemoprophylactic agents was not determined. Bacterial sensitivity studies are planned as part of a more extensive survey of the oral flora in patients receiving sulfadiazine prophylaxis against rheumatic fever.

I. Summary. Among 21 children receiving long-term sulfadiazine prophylaxis against rheumatic fever the only difference in the oral flora between this study group and the control group was an increased number of alpha streptococci. No significant difference in the occurrence of coagulase-positive staphylococci, *Neisseria*, lactobacilli, yeast, or fastiform bacilli and spirilla was noted.

major alteration in the oral flora was seen to result from sulfadiazine prophylaxis against rheumatic fever.

Annette Russ Wenger MD
Frederick Monroe Miller J D D S
Alice Brum M S
Department of Medicine
Emory University School of Medicine
Cardiac Clinics
Grady Memorial Hospital
Emory University School of Dentistry
State of Georgia Department of Public Health
Laboratories
Atlanta Georgia

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Sinus tachycardia complicating and outlasting pericarditis

Pericarditis is sometimes associated with sinus tachycardia which bears no relation to the degree of fever, severity of inflammation or congestive heart failure and often persists long after the inflammatory process has ceased.

The rate of sinus tachycardia in 6 cases of pericarditis which I observed ranged from 96 to 130 per minute. In 4 patients pericarditis was part of the postmyocardial infarction syndrome. In the fifth patient there was an idiopathic pericarditis of unknown etiology. In the sixth case in which chronic pericardial effusion of unknown cause had lasted for many years sinus tachycardia developed shortly after pericardiotomy. It persisted for 4 weeks until corticosteroids were given in an attempt to influence what appeared to be a postcardiotomy syndrome. A to duration sinus tachycardia was present

in one patient for a week, in another for 4 weeks and in a third for 8 weeks. In the remainder of the patients the duration was 2 months, 3 months and 6 months.

Sinus tachycardia was in most instances remarkably constant over periods of several weeks or months. In one patient it was temporarily lowered by Rauwolfia. In the severest case with sinus tachycardia up to 130 per minute lasting for 8 months a change to normal heart rate was observed during a short period of hospitalization. The patient, but sinus tachycardia returned after discharge. In this particular patient it was possible to slow down the heart rate temporarily by pressure on the carotid sinus area. In another patient who had suffered myocardial infarction and the appearance of sinus tachycardia which first

aroused as person of complicating pericarditis. This
as later substantiated by x-ray examination.

Recent studies by T. N. James shed light upon
the relationship of pericarditis and the sinus node.
The author pointed out that the sinus node and its
series because of superficial position in the heart
were commonly involved by pericarditis. This may
result in stimulation of the node and manifest
itself in sinus tachycardia, or the appearance of
various atrial arrhythmias, including atrial fibril-
lation. In the aforementioned case in which the
tachycardia lasted for 8 months attacks of atrial
fibrillation and frequent atrial premature beats
were observed. James drew attention to iatrogenic
pericarditis brought on by cardiac surgery or mas-
sage of the heart which may manifest itself by the
development of various disturbances in rhythm.

Knowledge of sinus tachycardia as an innocent
complication of pericarditis is important because
of the grave implication usually associated with this
disturbance. When seen in conjunction with heart
disease sinus tachycardia often considered to be
a sign of severe myocardial involvement or heart
failure. At a clinical pathological conference at the
Massachusetts General Hospital in which a case
of coronary arteriosclerosis with signs suggestive
of pericardial effusion was presented, one discuss-

ant remarked that after subjective and objective
improvement a per test and on many findings
was tachycardia with the rate never dropping be-
low 104 to 108 per minute. Indeed in the first 2
cases which I observed the appearance of sinus
tachycardia was cause of great concern lest it be
indicative of serious myocardial involvement. Later
experience did not substantiate this opinion. Pa-
tients with marked sinus tachycardia did not do
worse than other patients suffering from pericarditis
without complicating tachycardia. Even so the
presence of sinus tachycardia and protracted sinus
tachycardia the working capacity was strikingly
impaired.

William Dressler, M.D.
Department of Medical Services
Massachusetts General Hospital
Boston, Mass.

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A plea for atrial fibrillation

In addition to their passive role as reservoir, the
atria contribute through their contraction to ven-
tricular dynamics. It has long been known that
atrial systole increases end-diastolic ventricular
filling and pressure (provided that the P-R interval
is between 100 and 300 msec). This favors tight
closure of the atrio-ventricular valves and the ef-
ficiency of stroke volume and cardiac output. This
physiologic dogma has been based chiefly upon ex-
perimental work performed in the animal labora-
tory. The every perturbation disrupting the re-
lationship between the atria and the ventricle ad-
versely affects performance of the heart as a pump.
Thus holds of course for complete AV block. For
therefore countless contemporary publications
have stressed the deleterious effect of atrial fibril-
lation (AF) on ventricular function according to
evidence derived not only from animal experiments
but also from data gathered in the human cardiac
catheterization laboratory. Consequently it has
become commonplace to let AF as a disqualifying
factor in the selection of patients for sinus rhythm
(SR) as a permanent therapeutic goal. This
so much is of interest for the fact that it has
appeared in the literature only very recently
that a certain type of atrial fibrillation (AF) may
be converted to a normal sinus rhythm (SR) by
the administration of a certain drug.

was the method of choice for abolishing AF either
immediately or more commonly after digitalis had
lowered the ventricular response but failed to restore
SR by itself. Success was obtained in a fair percent-
age of cases, not infrequently at the cost of dis-
comforting side effect and occasionally periculo-
cardiac toxicity with death rate of 3 to 4 per-
cent. Nowadays, following the basic pioneering
work of Paul Zoll, outlining a new method of
direct-current countershock, has thoroughly trans-
formed the question. By means of this technique
of controlled cardioversion as described by Bernard Low,
AF can be suppressed with very low risk and
tolerable inconvenience to the patients. With a
light at the toll the growing trend toward broadly ex-
tending indications for cardioversion of AF appears
to be understandable and apparently sound.

Unfortunately, restoring SR is but the first
chapter in a long story for the main problem still
remains unsolved: that how to fully prevent
recurrence of AF as a permanent rhythm main-
tain the heart under the control of the sinus node.

Now several possibilities exist: (1) A fraction
of subjects spontaneously maintain SR without
any fibrillatory drug. (2) Some others stay
SR with small well tolerated daily dose of
quinidine. (3) But the majority of patients remain

International Society of Cardiology— The Research Committee at Venice, Italy

Annel Keys* Chairman

Research Committee I S C

The Research Committee of the International Society of Cardiology (I S C) is charged with the responsibility of informing, and extending, the activities of the Society in all matters of research relevant to the interests of the I S C. At the World Congress of Cardiology in Mexico City (October 1962) it was agreed that the I S C—until then concerned almost exclusively with organizing the periodic World Congresses of Cardiology—should be more active in the years between congresses. In particular it was agreed that the Research Committee of the Society should function between as well as during the congresses.

Accordingly the Research Committee was reconstituted at Mexico City with 21 members: 3 Corresponding Secretaries and 3 Liaison Representatives from 22 countries. The officers for 1962-1966 were: Honorary Chairman Paul Dudley White, Chairman Annel Keys, Vice Chairman Alberto Tiquin, Executive Secretary Jean Lequime. The Research Committee met at Mokaraka, Yugoslavia, Sept. 18-23, 1963 as reported in various journals (e.g., *British Heart Journal* 26:558-560, 1964; *Zeitschrift für Kreislaufforschung* 33:762-764, 1964; *Japanese Heart Journal* 5:189-193, 1964; *Acta Cardiologica* 19:303-320, 1964). The Research Committee met again at the Giorgio Cini Foundation, Venice, Italy, April 11-17, 1967. Notes on the

proceedings, currently published in more detail in *Acta Cardiologica*, are given below.

Venice meeting of the Research Committee

The Venice meeting was attended by representatives from 22 countries and the World Health Organization, 28 members of the Committee and Subcommittees, 14 Consultants, 3 members of the Committee of the 1966 World Congress at New Delhi, and 20 Observers. Items of note included the following:

I. Statement of the I S C for the World Health Assembly (Pierre Duchosal).

II. Report on organization of the World Congress of Cardiology at New Delhi (K. K. Datta, S. Padmanabhan, Sujay B. Roy).

III. Reports from Subcommittees of the Research Committee: (a) Epidemiology (J. Stamler), (b) Clinical Physiology (I. Wierko), (c) I S C, A C C, and Computer Applications (H. Blackburn).

IV. Reports on Symposia arranged by the Research Committee to be presented at the Congress in New Delhi (Dr. Henry Blackburn: Congestive Heart Failure; Dexter / Lejlar M. J. Karvonen: Hypertension; Maddox M. I. Oliver: Otto H. Schmitt; J. Stamler).

V. Report on World Health Organization Activities in Cardiovascular Diseases (Geneva HQ—/ Lejlar European Office—/ 1967).

VI Report from the International Cardiology Foundation (P. D. White and Howard Sprague)

I Statement of the I S C for the World Health Assembly (Pierre Duchosal)

Cardiovascular diseases continue to be major health problems throughout the world. They are responsible annually for the disability and death of tens of millions of all ages—children, adults in the prime of life and the elderly. They place a huge burden on the health services and their drain upon the economy of all countries is continuous and vast.

When fully established and manifest clinically as frank illness cardiovascular diseases significantly impair life expectancy. All too often they produce sudden and unexpected death. Therefore prevention—first and foremost primary prevention, also effective secondary prevention based on early detection—is the key to the successful control of the cardiovascular diseases.

At present a marked lag exists on a world scale between the acquisition of new knowledge concerning the prevention of cardiovascular diseases and the application of this knowledge in preventive programs. Moreover the research effort, particularly the epidemiologic research effort—essential for the development of more effective preventive measures—is grossly inadequate in terms both of the need and the potential. There is no doubt that a greatly expanded research effort at the international level proceeding first and foremost along epidemiologic lines could be mounted at present and could contribute significantly to early progress in the control and prevention of the major cardiovascular diseases. The studies in progress testify to this fact. At the same time they demonstrate by their limited nature the large gap between possibilities and actual investigative activities and the major unfilled needs for further research on the epidemiology of cardiovascular diseases and on methodology in this field. These unfilled needs reflect inadequacy of resources, first and foremost. This situation must be a matter of the most serious consideration for all responsible agencies in the field—the International Society of Cardiology, the national heart association, the

World Health Organization and the national health services.

In order at the earliest date to overcome present difficulties and to speed up scientific progress and public health advances against the cardiovascular diseases the International Society of Cardiology registers its full support for the proposed W H O International Research Center calls for its earliest possible establishment and urges that it give significant priority to research on the epidemiology, control and prevention of the cardiovascular diseases.

II Organization of the New Delhi Congress (K. K. Datta, S. Padmanabhi Sujan, B. Roy)

The Organizing Committee reported that the program for New Delhi adheres to the recommendations endorsed by the Council of the I S C of the Maharaja's meeting of the Research Committee. Plenary sessions with no other competing sessions will occupy the six mornings, October 31–November 5. Most of these plenary sessions will consist of symposia presented by invited experts on the subjects proposed by the Research Committee: (1) Current Status of the Study of Cardiopulmonary Function (Coordinator J. Lequeime); (2) Etiology and Pathogenesis of Cardiomyopathies (Coordinator A. G. Shaper); (3) Present Status of Prevention of Rheumatic Heart Disease (Coordinator R. Froment); (4) Precocious Ischemic Heart Disease (Coordinator Kempson M. J. Haddox); (5) Evaluation of Cardiovascular and Cardiopulmonary Function After Cardiovascular Surgery (Coordinator Lewis Dexter); (6) Exercise Tests in the Evaluation of Cardiovascular Function (Coordinator M. J. Karvonen); (7) Computers in Cardiovascular Disease (Coordinator Otto H. Schmitt); (8) Effect of Climate on the Cardiovascular System (Coordinator J. R. Lind).

IIIa The Epidemiology Subcommittee (J. Stamler, Chairman)

In various parts of the world there are unique opportunities to study hypertension and coronary heart disease in ethnic groups whose living conditions are changing and who differ in patterns of cardiovascular disease. These opportunities continue to be neglected. Immediate efforts should

made to explore research potential personnel facilities and financial support in order to improve the situation before irreplaceable opportunities are lost. It is proposed that a joint I S C - W H O panel be formed to this end.

Current epidemiologic research is providing significant data on the relationship of the incidence of coronary heart disease to several controllable factors: the diet, cigarette smoking, physical activity, blood pressure, and obesity. It is recommended that epidemiologic research on such factors be greatly intensified because of the important potentials for preventive programs.

Epidemiologic studies on peripheral vascular disease have lagged and should be encouraged. There is need for improved methods for estimating peripheral vascular occlusion and for studies to define relationships between peripheral vascular disease and other circulatory disorders.

Epidemiologic research on cerebrovascular disease has also been neglected until recently and even now the efforts are far from commensurate with the importance of the problems. The extent to which populations and population groups differ in susceptibility to cerebrovascular diseases is unknown. There is a great need for improved methodology, especially in the detection of cerebrovascular disease before catastrophic episodes.

Epidemiologic information is grossly deficient on chronic respiratory diseases and in the relationship of these disorders to cardiovascular diseases. Besides the relative lack of information on these questions, there is need for studies on the relative contributions in different populations of chronic bronchitis, emphysema, asthma, recurrent pulmonary embolism and air pollution. Improved objective methods for detection and evaluation of these conditions are needed.

In spite of considerable efforts rheumatic heart disease remains a major health problem especially in many parts of Asia, Africa and Latin America. Further epidemiologic work is needed on the relationship between streptococcal infections and rheumatic heart disease and on the special features in populations in which rheumatic heart disease is common but rheumatic fever apparently is not. There is need for more systematic use of the epi-

demologic method in the assessment of control programs.

Epidemiologic study of congenital heart disease has been neglected. There is little information about the extent of any of differences in frequency among populations or on relationships between congenital heart disease and controllable characteristics of the mode of life. In this area as in the other areas of circulatory disease noted above it is recommended that epidemiologic research be markedly increased and elevated to a totally new plane.

In this whole field of epidemiology much greater support is needed including stable long term financing to obtain basic data to develop improved methods to provide training programs and to expand work directed toward practical problems of prevention. In the epidemiology of circulatory diseases medical education is defective: there is a major gap between clinical and preventive medicine and there is a marked shortage of trained personnel. There is a serious need to develop and support training centers including at least one in a developing country. The proposal for an international center under the aegis of W H O is strongly supported. Organizations now actively engaged in research on cardiovascular epidemiology should be given support specifically for training both at their home headquarters and in field operations.

IIIb The Subcommittee on Clinical Physiology (Lars Werkö, Chairman)

The Subcommittee and its several working groups all emphasized the need for close collaboration with other international organizations with similar or adjacent fields of interest, notably W H O, the International Physiology Society and the International Biological Program. Conferences of similar groups on highly well defined topics are important and such meetings should be arranged between the large international congresses.

The area of responsibility of the Subcommittee on Clinical Physiology is so large that only selected topics were covered at Venice: (1) influence of thermal stress on the circulatory system, (2) results of cardiovascular surgery, (3) influence of exercise on cardiovascular function and disease, (4) system analysis in the study of the circulatory system.

An *ad hoc* group (L Dexter S B Roy R Margaria) advised that there are many unresolved questions about the circulatory effects of the hypoxia of high altitude and recommended that these be considered in depth on another occasion. The Subcommittee noted with satisfaction the activity of the international group on phonocardiography especially on standardization (K. Holmdahl).

1 THERMAL STRESS (George Burch A Sorocou M Poor A R Lind)

Cardiovascular responses to thermal stresses pose important problems which warrant much more clinical and scientific attention. About two thirds of the world's population is in tropical or subtropical climates but clinical standards in those areas as elsewhere derive from temperate zones. Among topics that deserve more discussion and study are cardiovascular problems in acclimatization to cold and to heat, cardiovascular problems in acute thermal stress, the effect of heat on the hemodynamics of cardiac patients, functional capacities of the cardiovascular system in populations living in hot climates, regional blood flow in exercise in heat, cardiovascular events in heat syncope, electrolyte balance in different climates.

2 RESULTS OF CARDIOVASCULAR SURGERY (Lewis Dexter John Shillingford Lars Werko)

A panel of eleven cardiologists each from a different country has been organized to make objective evaluations of the results of surgery for specific cardiovascular disorders. Arrangements were made for these experts to meet about 6 months before the New Delhi Congress and to present their findings in a symposium at the Congress. The disorders to be covered include patent ductus arteriosus, constrictive pericarditis, and each of the major defects of the valves and septa of the heart. In spite of interest in surgery for coronary heart disease and on coronary revascularization, it was thought that the time is not yet ripe to make a general assessment of the results of surgery in that area.

It was agreed that assessment of both immediate and long term results of cardiovascular surgery requires standardized procedures and recording. It is desirable also to determine the change in the natural

history of the disease occasioned by surgery. It was pointed out that there are striking differences in the severity and complications of these diseases in different parts of the world and allowance for these must be made in assessing the results of surgery.

3 EFFECTS OF EXERCISE (M J Karvonen)

The influence of exercise on the cardiovascular system particularly in relation ship to the epidemiology of coronary heart disease was selected at the Helsinki meeting of the Research Committee as a topic of prime current importance. In cooperation with the Finnish Heart Association a special conference of about 80 experts was held at Helsinki August 27-29, 1964, the proceedings of that conference are now in press (Charles C Thomas and Company Springfield Ill).

It was noted that lately there is much enthusiastic interest in the possibility of primary prevention of coronary heart disease by physical activity. The favorable evidence is largely from statistics on morbidity and mortality among men classified by occupation. However interpretation is clouded by occupational mobility and by the inherent obstacles involved in comparing self selected groups. There are also questions about differential bias in diagnosis when persons in disparate socioeconomic classes are compared. Finally occupational activity does not necessarily reflect total physical activity especially in the developed countries. It was agreed that extensive studies more critically designed and carried out are greatly needed in order to assess the possible role of physical activity or a lack of it in the etiology of coronary heart disease. Assessment of habitual physical activity is difficult and much needs improvement.

In the presence of established cardiovascular disease there is increasing evidence of the value of exercise in rehabilitation. However much research is needed to define the exact role of physical activity and to provide appropriate exercise prescription. Exercise tolerance tests should be useful in this respect as well as in diagnosis but as yet there is little agreement about the methodology to be used either with patients or in field.

Here again much new research is needed.

In the meantime there is interest in developing intervention programs involving physical exercise in the hope of preventing coronary heart disease. Feasibility studies are needed in order to appraise the possibilities for large scale trials.

4. SYSTEM ANALYSIS (Lasse Peterson and an *ad hoc* group with Z. Fejfar as recorder)

In cardiovascular clinical physiology there is an important place for system analysis i.e. the integration of cardiovascular and other functions in the body and the relationships of these with the environment. The trend is to put the body together again by the application of computers and related instruments to simultaneously collected data on several or even many variables. By these means models of integrated actions may be developed or multivariate analysis can reveal the combined effect of several variables on a single parameter. The Research Committee is much interested in these new approaches of system analysis and strongly urges that they be encouraged and made more widely known.

III: The Subcommittee on ECG ICG and Computer Applications (Henry Blackburn, Chairman, Pierre Duchosal, Noboru Sumori, Pankaj Rautbharju, Pierre Rayling and Consultants Hubert Pipberger and Otto H. Schmitt)

Theory based on sound biophysical principles leads to conclusions that render obsolete some concepts still commonly held in electrocardiography: (1) the concept of an absolute zero potential to which ECG leads can be usefully referred; (2) the concept of unipolar leads as distinct from bipolar leads; (3) the concept that frontal plane Leads I, II, III or leads derived from them by combinations (aVR, aVL, aVF, aVR, aVL, aVF) contain intrinsically more information than any pair of them selected at random; (4) the concept that the ventricular gradient has a physiological basis rather than being simply an empirical time integral of potential.

In ECG techniques much improvement is needed in the skin electrode contact in the recorder in procedural and instrumental standardization in modular design and in quantitative analysis. These points are treated in some detail and recom-

mendations made in the full report pp 17-23.)

Pioneering accomplishments have been made in the application of biophysical concepts and methods to electrocardiography notably in the attempts to provide corrected lead systems in utilization of FM tape recording and in powerful methods of measurement and analysis by computers. It is recommended that support be given to the orderly transition into effective application of these new tools. It is essential that the new methods retain the contribution to knowledge of the old and during the transition remain as nearly compatible as possible.

II. Reports on Symposia

The Subcommittee reports summarized above cover some of the symposium material arranged for New Delhi. Additional symposia sponsored by the Research Committee are noted below.

IIa. The Cardiomyopathies (Z. Fejfar)

Obscure forms of heart disease notably cardiomyopathies are present in all parts of the world but in tropical and subtropical countries these disorders constitute one of the major clinical and health problems. Studies on these questions are in progress in many places but cooperative research should be initiated and such studies need expression. It is recommended that in each cooperating area a cardiac register should be established and the research team should include a cardiologist, a radiologist, a pathologist and an epidemiologist. Particular attention should be paid to certain groups of patients: children, pregnant and puerperal women with any suspicion of heart disease, persons of any age with pericarditis, persons of any age with unexplained cardiomegaly. Each co-operating center should establish a serum bank covering all patients with cardiomyopathies.

At present population studies on prevalence or incidence of cardiomyopathies are not warranted but field studies would be useful for case finding and for testing certain hypotheses.

A symposium on the cardiomyopathies will be held at the New Delhi Congress.

IIb. Precocious Ischemic Heart Disease (M. J. Oliver & M. Addox)

In many prosperous areas coronary heart disease in persons under the age of

40 is sufficiently common to constitute a challenge. In order to define more accurately the magnitude of the problem cooperative international studies are needed. Among questions for special study are these: What are the features of the pathology in young patients? Is there any specific anomaly in the anatomy of the coronary system? Is the clinical presentation different from that in older patients? Is the contribution of ischemic heart disease to sudden death the same at different ages? What is the relative importance of different risk factors at different ages?

Although the importance of the prevention of precocious ischemic heart disease was universally accepted it was thought that more work is required to characterize younger persons at high risk before any large scale international preventive programs are initiated. On the other hand exploratory preventive trials should be encouraged especially on young men clinically healthy who appear to be at particularly high risk.

A symposium on precocious ischemic heart disease will be held at the New Delhi Congress.

III Computer Aided Quantitation (Otto H. Schmitt)

Comparison of the present state of medical science with electronic and computer technology shows a needless disparity. This is in part the result of a series of barriers that must be overcome if medical science is to take advantage of the paths of progress marked out by the physical sciences. These barriers concern (1) inadequate education both of medical students and of established investigators in mathematics, physics and electronic and computer sciences; (2) the need to move away from attachment to specialized instruments that communicate only to the individual investigator to system theory and the modular approach; (3) the need to develop sophisticated theory specifically for medical science rather than simply borrowing from available mathematical engineering and biophysical technology; (4) a lag in instrumentation and components for specifically medical purposes because medical science is not existing in the cost of design and development in any way comparable to that of industry and the military in nonmedical fields.

(5) the facing of the standards problem not simply in terms of agreed nomenclature but in terms of preferred values of parameters, formats for tape recording and in the devices and methods of acquisition of data.

Computer aided quantitation in regard to cardiovascular function and disease utilizing properly the advances in the physical sciences requires that these barriers be appreciated and overcome. A symposium on computers in cardiovascular disease will be held at the New Delhi Congress.

IV WHO Activities (Z. Fajlar (Geneva) and Z. Pasa (Copenhagen))

Both at Geneva in the world headquarters of WHO and at Copenhagen in the European office activities in the area of cardiovascular diseases are increasing. These activities include the organizing of conferences of experts on different aspects of cardiovascular diseases, stimulation of research programs, preparation of reports and handbooks on problems and methods, coordination of collaborative research programs and compilation of directories of centers for research and training in the area of cardiovascular disease. There are close official and personal connections between the WHO and the I S C.

VI The International Cardiology Foundation (Paul Dudley White, Howard Sprague)

The International Cardiology Foundation is establishing supporting groups in various countries and is becoming more directly affiliated with the I S C. A Geneva office to be established shortly will strengthen the link between the I S C and WHO as well as emphasize the truly international character of the Foundation. Among other activities the Foundation made possible the Nakurka and the Venice meetings of the Research Committee and has greatly helped in the preparations for the New Delhi Congress.

VII The Research Committee at New Delhi

The Research Committee of the I S C will meet at New Delhi on Oct. 29 and 30, 1966, i.e. immediately before the World Congress on Cardiology. Items that may be of interest to the Committee at this time should be transmitted to the Executive Secretary, Professor J. Lequime, 91 Av. Franklin Roosevelt, Brussels, Belgium.

Book reviews

VERHANDEN EN DER DUITSCHE GESELLSCHAFT FÜR KARDIOVASCULÄRE MEDIZIN. Edited by Prof. Dr. Ludolf Thauer and Prof. Dr. Claus Albers. Darmstadt 1965. Dr. Dietrich Steinkopff Verlag. 394 pages. Price DM 62.

This book is a report of the 31st Meeting of the German Society of Cardiovascular Research 1965, the main topic of which was 'cardiovascular insufficiency'. The book includes reports on anatomy, pathology, pathogenesis, hemodynamics and diagnosis as well as conservative and surgical treatment of 'valvular insufficiency'. Besides these one finds numerous short reports on independent selected topics as well as a chapter 'training and education about acute arterial obstruction'. Because of the large number of authors the standard of the individual contribution is low. The reports under the main topics provide comprehensive surveys of the pathophysiology as well as clinical and operative discussion of the results of surgery. The 'non-unique' of aorta and mitral insufficiency

portance of the trauma which the major surgical procedures associated with the implantation of such pumps inflict upon a failing heart. In fact there was an impressive absence of cardiologists and cardiovascular physiologists attendant upon the symposium thus providing a background of bias. It is well known that major physical trauma and surgery are precipitating causes of congestive heart failure. The role of these procedures and their importance should have received more consideration. The day will surely arrive when the circulation of man can be assisted with benefit but the symposium will impress the knowledgeable reader with the remoteness of this in spite of recent publicity and sensationalism and the misleading of such cardiac patients. This symposium is of interest but those who follow the literature in cardiology will find little new and the thoughtful reader will be aware of many important problems not considered. Symposiums of this sort, a type commonly held in the United States today, do serve a useful purpose, however

MECHANICAL DEVICES TO ASSIST THE FAILURED HEART. Proceedings of a Conference National Academic Sciences-National Research Council Washington D.C. 1966. 287 pages. Price \$9.50 (National Academy of Sciences Publication No. 1283).

This report is the proceedings of a symposium held on Sept 9 and 10 1964 under the auspices of the National Research Council and its Committee on Pumping. The symposium is divided into three parts: one concerned with physiology, another with pumps and the third with cardiovascular disease. There are presentations related to oxygenation, left heart assistance with pumps and counterpulsation experiments with patients and a description of various types of pumps as well as mechanical and physiologic problems connected with the use of pumps to assist the heart. This symposium reflects the thinking and progress at the time as well as the depth of the considerations. There are many illustrations and much discussion but the symposium reveals an inadequate consideration of the basic physiologic, pathologic and cardiologic problems related to congestive heart failure as well as to the circulation in general. Surely such studies are to be encouraged but to try these pumps in patients who might continue to live a year or more without excellent cardiologic care certainly cannot be accepted by all physicians who have established a close patient-physician relationship. Such aspects of the practice of medicine were not discussed nor was the extreme im-

CONGENITAL HEART DISEASE: AN ILLUSTRATED DIALECTIC APPROACH. By Saul J. Robinson M.D. Clinical Associate Professor of Pediatrics, Stanford Cancer by Herbert L. Abrams M.D. Professor of Radiology, Stanford University and Henry S. Kaplan M.D. Professor, Department of Radiology, Stanford University. Ed 2 New York 1965. McGraw-Hill Book Company Inc. 248 pages. Price \$19.50.

This is the second edition of a book first published in 1954. The current edition represents a moderately extensive revision and amplification. The book is presented in two sections. The first deals with clinical evaluations, routine and special laboratory procedures and treatment of congenital heart disease in general. The second section is an atlas form and covers the specific congenital cardiac defects.

It is difficult for this reviewer to make a recommendation to potential readers regarding this relatively short book. It is a work in which group stands to profit from the material presented here. It is of worth not for the cardiologist or for the internist primarily oriented toward cardiology. To other groups with an interest in congenital heart disease there may be something of value. For them the book would provide a concise and lucid but not profound review of the problem. Particularly valuable is a short but well-chosen bibliography.

THE PATHOGENESIS OF CARDIAC CACHEXIA By Joseph G. Pittman MD Research Fellow in Medicine Massachusetts General Hospital and Harvard Medical School and Elvin Cohen MD Associate in Medicine Peter Bent Brigham Hospital and Harvard Medical School Boston Mass New York 1965 Grune & Stratton Inc 88 page Price \$3.25

This book focuses attention on the pathogenesis of the cachexia that often accompanies chronic long-standing congestive heart failure. The increasing importance of this relatively neglected clinical problem is underscored by recent medical and surgical advances in the treatment of heart disease which have prolonged considerably the lives of many cardiac patients. Dr. Pittman and Dr. Cohen describe the pathogenesis of cardiac cachexia in terms of dietary factors metabolic abnormalities associated with congestive heart failure abnormal losses of nutrients and autogenic factors. These contributory causes are the subject of detailed analysis in this carefully written and extensively documented monograph. Therapeutic problems are considered only very briefly.

history and physical examination supplemented by a few relatively simple laboratory studies. The book is divided into two sections the first of which describes specific applications of the techniques of clinical examination and laboratory procedures to the evaluation of chest pain. The second section is devoted to clinical pathologic and therapeutic considerations of the various causes of chest pain which is classified according to anatomic origin including pain originating in structures of the thoracic wall thoracic viscera mediastinum shoulder girdle head neck and abdomen and from a number of miscellaneous syndromes that have no topographic localization. The material is presented in a concise manner with emphasis on conditions that are either unfamiliar or likely to be overlooked by the diagnostician.

This is a valuable book for physicians and medical students.

Books received

PAIN IN THE CHEST By William H. Wehrmacher MD FACP FACC Northwestern University Medical School Chicago 111 Springfield Ill 1964 Charles C Thomas 403 pages Price \$14

Problems in the differential diagnosis of chest pain are the subject of detailed discussion in this highly readable book. Dr. Wehrmacher rightly emphasizes the fact that in most instances the etiology of chest pain can be established on the basis of a meticulous and systematic clinical

✓ **REPRODUCTION MOLECULAR SUBCELLULAR AND CELLULAR** Edited by Michael Locke New York 1966 Academic Press Inc 344 pages Price \$11.50

PRINCIPLES OF HEMATOLOGY By Jerome W. Luzzman New York 1966 The Macmillan Co 671 page Price \$12.50

ADVANCES IN RESPIRATORY PHYSIOLOGY Edited by Colin G. Caro Baltimore 1966 The Williams & Wilkins Company 348 pages Price \$17.50

Editorial

Coronary arteriography

Richard S. Ross, MD
G. C. Friesinger, MD**
Baltimore, Md

The contributions of many, but especially those of Mason Sones, have made it possible to obtain excellent visualization of the coronary arteries in conscious man under circumstances which are close to physiologic normality. Adequate visualization of the coronary tree requires multiple selective injections of the coronary arteries with the patient in different positions. Visualization after the administration of a coronary vasodilator is also helpful. Highly specialized radiologic and photographic equipment is required, and both professional and technical personnel must be well trained.

Radiologic and photographic techniques have improved progressively, and relatively minor anatomic lesions can now be detected; hence problems of interpretation have now assumed great importance. The significance of arteriographic findings depends to a large extent upon the population under study, and this in turn depends on indications for study. For this

reason, it is worth while to consider the indications which are currently employed in most laboratories. The majority of the patients subjected to coronary arteriography fall into two groups on the basis of indication for study. The first group of patients commonly studied (in 1965) are those who have typical angina pectoris, which is disabling and unresponsive to medical therapy. These patients are studied to select those who may be helped by surgical therapy. The second group of patients have chest pain which is not typical angina pectoris and which therefore is of uncertain origin. In this editorial we are concerned with patients in this second group in whom the arteriography is being performed as a diagnostic test.

One of the problems in the interpretation of the coronary arteriogram as a diagnostic test appears to stem from an imprecise definition of terms. The authors think that the diagram in Fig. 1 is useful in defining

From the Department of Medicine, Johns Hopkins Hospital, Baltimore, Md. Received by the Journal for publication July 11, 1966. Accepted for publication September 11, 1966. Address reprint requests to Dr. Ross, Department of Medicine, Johns Hopkins Hospital, Baltimore, Md. 21205. *Present address: Department of Medicine, University of Maryland School of Medicine, Baltimore, Md. **Present address: Department of Medicine, University of Maryland School of Medicine, Baltimore, Md. 21205. Copyright © 1966 by W. B. Saunders Company. Printed in the U.S.A.

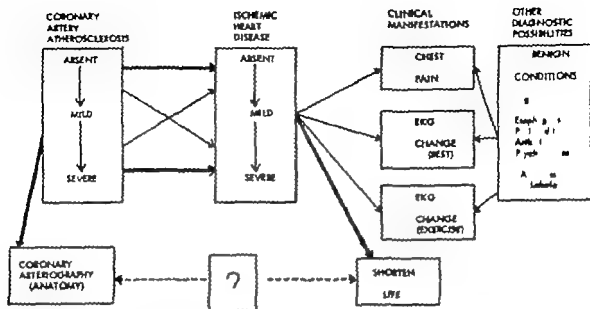


Fig. 1 Diagrammatic representation of the relationship between coronary artery atherosclerosis and ischemic heart disease. The clinical manifestations of ischemic heart disease which usually result in the patient's presentation as a diagnostic problem are listed.

terms and outlining the problems posed by the patient who may have ischemic heart disease. The essential feature of the problem is the aspiration of coronary artery atherosclerosis from ischemic heart disease as indicated by two blocks on the left hand side of the diagram. Coronary atherosclerosis is a disease process involving the coronary arteries. It may be mild, severe or absent. In Americans and most other Western people it is regularly present in adult males, progresses predictably with advancing age and has a propensity to localize in certain areas of the coronary tree.⁴ This pathologic process in the coronary arteries is usually, but not always, responsible for ischemic heart disease.

Ischemic heart disease is defined as the disease of the myocardium which usually develops as a consequence of coronary atherosclerosis and declares itself clinically by the development of angina pectoris, myocardial infarction or electrocardiographic changes. The most important of all the manifestations of ischemic heart disease is its propensity to shorten life and this aspect of the disease justifies all the thought and study devoted to it in recent years.

Let us examine the relationship between

coronary atherosclerosis and ischemic heart disease as depicted in Fig. 1. If there is no coronary atherosclerosis there will be no ischemic heart disease. If at the other extreme there is severe coronary atherosclerosis ischemic heart disease will usually, but not always, be present. Thus at the extremes of the spectrum a good relationship exists between the degree of coronary atherosclerosis and the presence of ischemic heart disease as indicated by the heavy arrows in the figure.

The patient usually is referred for evaluation because of chest pain or another clinical manifestation (Fig. 1) which may be due to ischemic heart disease. The diagnostic problem arises because the clinical manifestations are not easily identified with certainty as being due to ischemic heart disease. One or more of the conditions indicated as benign may be responsible. The physician needs to know whether the clinical manifestations are related to ischemic heart disease which will shorten the patient's life or to a benign condition which will not influence his longevity. Although arteriography is performed to determine whether the patient has ischemic heart disease, the study can only provide information about the

anatomy of the coronary arteries and the extent of the atherosclerotic process and does not directly detect or quantitate ischemic heart disease.

A consideration of the sensitivity of the arteriographic method is essential to any discussion of interpretation. The degree of atherosclerotic disease which need be present to be detected arteriographically in intact man has not been defined precisely, but available data indicate that luminal narrowing of 20 per cent will go undetected and more severe degrees of reduction in vessel size may not be appreciated if such narrowings are circumferential, cylindrical and smooth.¹¹

The arteriographic findings to be expected and the interpretation of the arteriogram will be importantly influenced by the population selected for study. Age is an important factor. It has been demonstrated that histologic changes of coronary atherosclerosis are frequently present in young adult males.¹² However, postmortem correlation of the histologic and arteriographic findings suggests that appreciable arteriographic alterations in asymptomatic individuals under 45 to 50 years of age must be very uncommon.¹³ In addition, postmortem studies have shown the pathologic changes in the coronary arteries to be regularly severe and multiple when ischemic heart disease is present.¹⁴ Hence an arteriographically normal coronary tree is very strong evidence against the presence of ischemic heart disease in this age group (under 50). Conversely, the atherosclerotic alterations seen in a large segment of the population over 60 years of age make it hazardous to attribute complaints of atypical chest pain to ischemic heart disease in a patient in this older age group who is shown to have minor abnormalities. Typical angina pectoris is regularly associated with severe pathologic changes and the instances in which the arteriogram did not disclose prominent changes in individuals with classic angina pectoris have been very rare in our experience. Similarly, we have never failed to demonstrate changes on the arteriogram of individuals with a history of myocardial infarction and residual electrocardiographic changes. Arteriographically normal coronary vessels have been demonstrated in individual with a

good history of a myocardial infarction with accompanying enzymatic alterations but without permanent electrocardiographic changes or the development of angina pectoris. We suspect that such individuals are unusual but are convinced that we have studied three such cases. We presume that these patients either experienced a twig thrombosis in the absence of diffuse and/or severe disease or occluded and then totally recanalized a larger vessel. The latter possibility seems to be the least likely. The prognosis in these cases is probably good.

With these observations in mind let us look again at the schematic representation in Fig. 1. The bold arrows connecting coronary atherosclerosis and ischemic heart disease indicate the usual relationships at the extremes of the spectrum. The thin arrows indicate that other relationships are possible as suggested by the experience cited above. For example, severe ischemic heart disease as evidenced by a myocardial infarction can result from atherosclerosis which is arteriographically mild; on the other hand, it is possible that severe atherosclerosis can be present and not result in ischemic heart disease if there are adequate collateral channels.

Coronary arteriography is most useful when it is used in conjunction with other methods of evaluation of the patient with chest pain. Most important in this regard is thoughtful and detailed and usually repeated history taking in difficult cases. In addition, exercise electrocardiography as outlined by Sheffield and Reeves¹⁵ is a useful adjunct. Although resting electrocardiographic changes may be the result of some of the benign conditions confused with ischemic heart disease, a truly positive ischemic electrocardiographic response to exercise has few, if any, other explanations. The combination of a normal coronary arteriogram and a negative exercise test makes it extremely remote that the patient's complaint of recurrent chest pain is attributable to ischemic heart disease.

The physician's duty extends beyond the exclusion of ischemic heart disease as a source of the patient's pain to the identification of the true cause of the symptoms. Esophagitis, common, produces symp-

toms that are confused with those of ischemic heart disease but it is only one of a long list of diseases which constitutes the differential diagnosis of chest pain. Prominent on this list is cardiac neurosis which is prone to become established because of the long duration of the complaints, the contact with many physicians and the inability or unwillingness of physicians to take a firm stand.

The diagnostic value of coronary arteriography will be enhanced by the completion of studies currently in progress which are designed to correlate the arteriographic findings with clinical manifestations and duration of life. Such correlations will bridge the gap between the arteriogram which quantitates coronary atherosclerosis and manifestations of is-

chemic heart disease which are of clinical importance.¹ An example of such a study is seen in Table I which shows the results of our experience correlating the type of chest pain with arteriographic findings. All patients were referred for evaluation because one or more physicians had made a diagnosis of ischemic heart disease. It is to be noted that the majority of patients with typical angina pectoris have severe degrees of coronary artery atherosclerosis. At the other extreme when the pain is clearly not angina pectoris a positive arteriogram is unusual. The arteriogram makes its major contributions in the group with atypical chest pain. These patients who have at least one feature of typical angina pectoris but not all three features are found to have arteriograms that range from revealing complete normality to showing the most severe atherosclerosis. Thus it is in this group that the arteriogram is helpful in identifying patients with severe disease who on the basis of history alone are indistinguishable from those with minimal or no disease. It is incorrect to assume that because the pain is atypical any coronary disease which is present will be of minor degree. The completed analysis of a larger experience will hopefully make it possible to define the minimal arteriographic lesion which can be responsible for significant symptoms of ischemic heart disease.

The most important and significant manifestation of ischemic heart disease, its tendency to shorten life, should be a factor which correlates with coronary arteriographic findings. We are making a study of such correlation. The goal of this study will be the development of tables which can be used to estimate the duration of life of a patient with a given arteriographic finding. Such an analysis may be the only means by which therapeutic maneuvers can be adequately assessed. Actually it is widely appreciated that there may be no means by which therapy can truly be evaluated in patients with ischemic heart disease in whom the propensity to develop a collateral circulation is unpredictable and yet so critical in determining prognosis. Data relating the arteriographic findings, including the presence of collateral vessels, to the prognosis

Table I

	Arteriographic class				
	1	0	2	3	4
Typical angina pectoris	7	11	5	11	21
Atypical angina pectoris	6	4	4	5	6
Ischemic pain	4	4	3	2	2
Nonischemic pain	19	4	2	2	0

Arteriographic classification

- 0 No atherosclerosis
- 1 Minimal abnormalities
No lesion narrowing > 50 per cent
- 2 Multiple severe narrowings > 50 per cent
- 3 One or more total obstructions

Chest pain classification

- 1 Typical angina pectoris: Pain which is
(1) Clearly precipitated by exertion and relieved by rest
(2) Deep visceral pain described as heavy squeezing, a burn, etc.
(3) Lasts some portion of the sternum

Atypical or nonanginal pain: Pain which has one or two but not all three of the properties of typical angina pectoris as described above but which still probably can be felt to be of ischemic origin.

Nonanginal pain: Pain which two clinicians agree is not anginal.

Unexplained pain: Pain which two clinicians classify into any of the three groups above or about which two clinicians disagree.

in individuals who have not received any specific form of therapy will certainly be the only means of assessment of a variety of surgical techniques which are currently being tried. The surgical procedures may relieve symptoms but if they are truly improving myocardial circulation they should increase life expectancy.

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Isolated abnormalities in high precordial leads, an infrequent sign of myocardial infarction

Morton Lee Pearce MD*

Warren Rosowsky MD

Raphael Levine MD

Los Angeles Calif

In 1946 Rosenbrum, Wilson and Johnston¹ suggested that unipolar leads from the high left thorax be taken when Leads I or aVL suggest a myocardial infarction but the 6 standard precordial leads fail to demonstrate the expected QRS changes. Other workers²⁻⁴ have also made this suggestion but in their studies as in those of the Wilson group, intomatic confirmation of the electrocardiographic diagnosis of high lateral infarction has been infrequent.

The purpose of this report is an evaluation of the usefulness of high precordial leads in establishing a diagnosis of high lateral infarction in patients whose limb leads (I or aVL) suggest this possibility but whose standard precordial leads do not confirm the diagnosis. The study is based on 20 patients whose electrocardiograms met these criteria and who later came to autopsy.

Methods

Since 1959 all patients with a conspicuous Q wave in Leads I or aVL of the conventional 12 lead electrocardiogram have had an additional 6 chest leads taken two

intercostal spaces above the conventional leads. We have found that the complexes recorded from these positions are reproducible in the hands of our technicians. All electrocardiograms were taken with a direct writing electrocardiograph at a paper speed of 25 mm per second. Two hundred and eighty six of these patients have come to autopsy. 20 of these had Q waves in Leads I or aVL which were not present in the standard precordial leads and Q waves in their high precordial leads. Since one of the two patients with infarction had only an isolated QS of 0.08 second in the high V₂ lead a QS or QR with a 0.04 second Q wave in the high V₂ lead or lateral to it were the minimal criteria for inclusion.

Results

Of the 286 autopsied patients reviewed 20 displayed the expected QRS changes of infarction in the high precordial leads without demonstrating any diagnostic abnormality in the standard precordial leads.

In 18 of these 20 cases the electrocardiographic diagnosis of infarction could not be substantiated at autopsy. Two cases

From the Veterans Administration Center, Los Angeles, Calif. and U. S. Department of Medical University of California, Los Angeles, Calif. Health Sciences at Los Angeles, Los Angeles, Calif.

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Address reprint requests to Dr. M. L. Pearce, Veterans Administration Center, 116th and Santa Monica Blvd., Los Angeles, Calif. 90062.

Table 1 Descriptions of leads I aVL and high precordials in 18 patients without infarction and in 2 patients with infarction

Lead number	I—T	I—aVL	Depth (mm) Q—T	Disturbance Q—aVL	Depth (mm) Q—T	I—T	I—aVL	High precordial leads				
								I ₁	V ₁	I ₂	V ₂	V ₃
Eighteen patients without infarction												
1	—	—	—	0.04	—	—	—	QR	QR	QR	QR	QR
2	—	—	—	0.04	—	—	—	QR	QR	QR	QR	QR
3	—	—	0.25	0.01	0.25	—	—	QR	QR	QR	QR	QR
4	—	—	0.25	0.09	0.25	—	—	QR	QR	QR	QR	QR
5	—	—	0.01	0.01	0.01	—	—	QR	QR	QR	QR	QR
6	—	—	0.07	0.07	0.07	—	—	QR	QR	QR	QR	QR
7	—	—	—	0.03	—	—	—	QR	QR	QR	QR	QR
8	—	—	0.25	0.03	0.25	—	—	QR	QR	QR	QR	QR
9	—	—	0.02	0.05	0.02	—	—	QR	QR	QR	QR	QR
10	—	—	0.07	0.03	0.07	—	—	QR	QR	QR	QR	QR
11	—	—	0.02	0.04	0.02	—	—	QR	QR	QR	QR	QR
12	—	—	—	0.03	—	—	—	QR	QR	QR	QR	QR
13	—	—	0.02	0.05	0.02	—	—	QR	QR	QR	QR	QR
14	—	—	—	0.04	—	—	—	QR	QR	QR	QR	QR
15	—	—	0.03	0.01	0.03	—	—	QR	QR	QR	QR	QR
16	—	—	—	0.02	—	—	—	QR	QR	QR	QR	QR
17	—	—	—	0.02	—	—	—	QR	QR	QR	QR	QR
18	—	—	—	0.02	—	—	—	QR	QR	QR	QR	QR
Two patients with infarction												
1	—	—	—	0.01	—	—	—	QR	QR	QR	QR	QR
2	—	—	—	0.01	—	—	—	QR	QR	QR	QR	QR

showed changes in the high precordial leads which were not seen in the conventional chest leads and had infarcts. One of these two had 0.02 second Q waves in Leads V_1 , which were 1 mm deep followed by sharp R waves. The high precordial leads showed 0.09 second QS waves in Leads V_1 . Autopsy revealed an extensive anterior infarct from the base to the apex extending into the lateral wall. The posterior surface showed patchy fibrosis. In the second case there were no Q waves in the standard precordial leads although the high precordial leads showed a QS in Leads V_1 , and a 0.02 second Q wave in Leads V_2 , less than 0.5 mm deep. There was a 2 cm subendocardial infarct high on the anterior wall. Electrocardiographic Leads I, aVL and the high precordial leads are described in Table I.

The electrocardiogram of one patient who had a high anterolateral infarct at autopsy showed a left ventricular conduction defect and Q waves were not present in the standard or high precordial leads.

Discussion

Rosenbaum, Wilson and Johnston¹ reported 6 cases of suspected infarction of the basal parts of the lateral wall of the left ventricle in which the conventional 12-lead electrocardiogram failed to establish definitively a diagnosis of myocardial infarction but in which unipolar leads from points on the anterolateral, lateral and posterolateral aspects of the upper left thorax supplied ECG data of greater diagnostic value. There was no autopsy confirmation in any of these cases.

In a later communication² these same authors stated that the electrocardiographic pattern of high anterolateral wall infarction shows diagnostic changes in Leads I or aVL and in unipolar leads from parts of the left side of the precordium or of the anterior surface of the left side of the chest that are nearer the left shoulder than those from which Leads V_1 , V_2 and V_3 are taken. The complexes of some of the standard leads from the left side of the precordium in abnormal but show much less pronounced changes than those exhibited by the leads mentioned.

In 1949 Myers and associates suggested

that infarcts confined to the interior, lateral and posterior aspects of the base of the left ventricle which could not be recognized by employing the standard Wilson leads could be recognized by using high thoracic leads. These authors reported 14 cases of autopsy proved high lateral infarction. The infarct was subepicardial in one case, transmural in 5 and subendocardial in 8. High leads at the level of the third intercostal space were obtained in 4 patients who were followed to autopsy and in one case the high precordial leads showed a diagnostic Q wave not seen in the standard precordial leads.

Further support for the use of high leads was given when Prinzmetal, Henner and Musumeci³ studied the high chest leads in a large number of normal subjects and in 66 patients with myocardial infarction and reported 6 instances in which the use of the high leads helped to establish the diagnosis of infarction. Again in these cases there was no autopsy confirmation.

Roesler⁴ suggested that T wave changes in the high precordial leads might be of value in the diagnosis of minor infarctions and Singer⁵ reported 3 cases of high infarction with changes in high precordial leads which were not seen in the standard precordial leads including one case substantiated at autopsy.

Our own data suggest that high precordial leads are of little value in the diagnosis of infarction and that the electrocardiographic changes are usually due to other causes. Rosenbaum, Wilson and Johnston¹ thought that the electrocardiographic changes were usually due to infarction of the parts of the wall of the left ventricle which are closer to the base of the chamber than those more commonly involved but did suggest that the abnormalities are sometimes the result of rotation of the heart or of some other change in the spatial relationships of its surface to the standard electrocardiographic leads. It should be noted that our 18 patients without infarction do not represent a normal population. Most of them were elderly men with a variety of illnesses. Prinzmetal and co-workers³ studied a normal population with high leads from V_1 through V_4 and found that Q

waves were rare in the high V_2 through V_4 positions.

This study suggests that infarction of the base of the left ventricle is the exceptional reason for the electrocardiographic abnormalities noted with the use of high precordial leads when the standard precordial leads fail to show them.

Summary

The electrocardiograms of 286 autopsied patients with Q waves in Leads I or aVL, who had high precordial leads taken were reviewed. Twenty patients displayed QRS changes of infarction in the high precordial leads without demonstrating any diagnostic QRS changes in the standard precordial leads. In only two instances was the electrocardiographic diagnosis supported at autopsy. It is suggested by this study that myocardial infarction is the exceptional cause for the electrocardiographic abnormalities seen only in the high precordial leads.

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Accuracy of preoperative diagnosis in congenital heart disease

Carlos Pestana M.D. Ph.D.*

William H. Weidman M.D.**

H. J. C. Swan M.B. Ph.D.***

Dwight C. McGoon M.D.****

Rochester, Minn.

Successful cardiac surgery depends to some degree on a correct preoperative diagnosis. However many inaccuracies in the diagnosis can be discovered at operation by the experienced surgeon and the proper repair completed with minimal or no inconvenience to the surgeon or increased risk to the patient. On the other hand certain errors in preoperative diagnosis can have a catastrophic effect on the outcome of an operation. This study was undertaken to evaluate the accuracy of the preoperative diagnosis of the condition of patients undergoing cardiac surgery for congenital defects and to determine the incidence of errors that significantly affect the success or safety of cardiac surgical procedures.

Method

We reviewed the records of all patients having a final surgical diagnosis of congenital heart disease who were operated on at the Mayo Clinic from July 1963 through June 1964; a total of 358 patients. Special attention was paid to diagnosis made after cardiac catheterization performed elsewhere and after clinical evalua-

tion and cardiac catheterization performed at the Mayo Clinic. We shall use the term clinical diagnosis to designate the diagnosis made from the history, physical examination, roentgenograms and electrocardiograms but without the benefit of cardiac catheterization.

Of the 358 patients 162 had been referred to the Mayo Clinic with a diagnosis that had been established elsewhere by cardiac catheterization. Since these patients represent a heterogeneous group in which the indications for and technique of cardiac catheterization were not uniform, they will not be discussed in detail.

The other 196 patients who had not had a cardiac catheterization previous to their visit to this clinic provide the material on which our results are based. Their ages ranged from 10 days to 65 years.

Results

The 196 patients were divided into three groups. The first group comprised 106 patients (54 per cent) for whom operation was advised on the basis of clinical diagnosis only. Cardiac catheterization was

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*Section of Internal Medicine, Mayo Clinic and Mayo Foundation.

**Section of Physical Diagnosis, Mayo Clinic and Mayo Foundation.

***Section of Pediatrics, Mayo Clinic and Mayo Foundation. Address correspondence to Section of Pediatrics, Mayo Clinic, Rochester, Minn. 55905.

not considered to be necessary for the establishment of a diagnosis in these cases although such a study was carried out in 22 of them in order to obtain supplemental information relative to physiologic or anatomic variables. Patients were retained in this group even if subsequent catheterization established an additional or alternative diagnosis and in this paper and its tables the diagnosis established before catheterization was retained as the preoperative diagnosis. The second group comprised 60 patients (31

per cent) for whom the clinical diagnosis was somewhat insecure and cardiac catheterization was considered to be necessary to establish the diagnosis. The third group comprised 30 patients (15 per cent) for whom a plausible clinical diagnosis could not be made and diagnosis was attempted only after cardiac catheterization and angiocardiology.

Group 1—Accuracy of preoperative diagnosis established by clinical means only. Eighty-five (80 per cent) of the 106 clinical diagnoses were found at operation to be

Table I. Cases found at operation to have a completely accurate preoperative diagnosis

Preoperative diagnosis	Cases having correct diagnosis		
	Group 1	Group 2	Group 3
Tetralogy of Fallot	18	4	2
Ventricular septal defect	13	5	2
Coarctation of the aorta	13		
Atrial septal defect	12	13	2
Patent ductus arteriosus	10	3	1
Aortic stenosis	8	2	2
Pulmonary stenosis	5		
Atrioventricular canal	3	3	
Total anomalous pulmonary venous connection	1	3	2
Vascular ring	1	1	
Pulmonary stenosis and atrial septal defect	1	1	1
Transposition of great vessel	1	1	
Ventricular septal defect and coarctation of aorta	1	2	
Aortic stenosis and coarctation of aorta	1	1	1
Ventricular septal defect with mild pulmonary stenosis		3	1
Ventricular septal defect and patent ductus arteriosus		3	
Left-coronary-to-right atrium fistula		1	
Atrial septal defect and patent ductus arteriosus		1	1
Coarctation of aorta and patent ductus arteriosus		1	
Tetralogy of Fallot and atrial septal defect		1	
Tricuspid stenosis		1	1
Aortic stenosis and patent ductus arteriosus			1
Coarctation of aorta and hypoplastic right ventricle			1
Pulmonary stenosis and tricuspid insufficiency			1
Transposition of great vessel with ventricular septal defect and coarctation of aorta			1
Common atrioventricular canal, coarctation of aorta, patent ductus arteriosus, and isolated levocardia			1
Aortopulmonary window			1
Transposition of great vessels with ventricular septal defect and pulmonary stenosis			1
Tetralogy of Fallot with left pulmonary artery arising from patent ductus arteriosus			1
Coarctation of aorta, dextroposition of heart, atrioventricular septal defect, stenosis of left pulmonary artery, hypoplasia of right pulmonary artery, and grossness of the right upper lobe artery			1
Total	85	50	25

Table 11 Additional unsuspected lesions found at operation

Inoperable diagnosis	After it was an diagnosis made at operation		
	Group 1	Group 2	Group 3
Tetralogy of Fallot	Agenesis of left pulmonary artery, persistent left superior vena cava, absence of inferior vena cava † Right pulmonary artery arising from ascending aorta Atrial septal defect Atrial septal defect Atrial septal defect Tricuspid stenosis and atrial septal defect		
Atrial septal defect	Mild mitral insufficiency Mild tricuspid insufficiency	Mild mitral insufficiency Anomalous pulmonary venous connection Anomalous pulmonary venous connection	
Ventricular septal defect	Partial atrioventricular canal Mild mitral insufficiency Infundibular stenosis	Patent ductus arteriosus Mild pulmonary stenosis Possible double outlet of right ventricle	
Pulmonary stenosis	Infundibular stenosis Infundibular stenosis Mild pulmonary stenosis		
Patent ductus arteriosus	Ventricular septal defect † Ventricular septal defect		
Coarctation of aorta, ventricular septal defect and patent ductus arteriosus	Only coarctation of aorta		
Coarctation of aorta alone	Patent ductus arteriosus Patent ductus arteriosus		
Partial atrioventricular canal	Atrial septal defect of secundum type	Atrial septal defect of secundum type and anomalous drainage of coronary sinus No atrial septal defect Grade 2 mitral insufficiency Patent ductus arteriosus No ventricular septal defect	
Anomalous pulmonary venous connection and atrial septal defect			No atrial septal defect
Double aortic arch			Mild infundibular stenosis
Ventricular septal defect, atrial septal defect and pulmonary stenosis			Infundibular stenosis not valvular
Tetralogy of Fallot and atrial septal defect			Interruption of aortic arch
Ventricular septal defect and coarctation of aorta			
Ventricular septal defect and mild pulmonary valve stenosis			
Ventricular septal defect and patent ductus arteriosus, probably coarctation of aorta			
Ventricular septal defect, patent ductus arteriosus, possibly atrial septal defect			Tricuspid insufficiency

Course of operation also recorded.

†Catheterization was carried out in 3 cases to determine the position of the ductus arteriosus.

completely accurate. The diagnoses in these 85 cases are listed in Table I.

In 21 (20 per cent) of the 106 cases the clinical diagnosis was confirmed at operation but an additional clinically unsuspected lesion was also present. In 17 cases the additional lesion did not materially alter the operation and accurate foreknowledge of its presence was not considered to be important. In 4 cases the additional lesion was of major importance. These lesions are listed in Table II.

In no case was the clinical diagnosis completely erroneous.

Group 2—Accuracy of preoperative diagnosis suspected by clinical means but established by catheterization. The preoperative diagnosis suspected clinically but established by cardiac catheterization was found at operation to be completely accurate in 50 (83 per cent) of the 60 cases that comprised this second group. These 50 cases are listed in Table I.

In 10 of the 60 cases the preoperative diagnosis was correct but an additional unsuspected lesion was found at operation. In 9 cases the presence of this additional lesion did not materially alter the operation but in 1 it resulted in an unnecessary ventriculotomy in that a ventricular septal defect had been diagnosed in addition to an atrial septal defect and mild pulmonary artery stenosis but in fact no ventricular septal defect was present.

In none of these 60 cases was the diagnosis completely erroneous.

Group 3—Accuracy of preoperative diagnosis established only by cardiac catheterization. Of the 30 patients in this group 25 (83 per cent) were found at operation to have lesions exactly as predicted in the preoperative diagnosis. These 25 cases are listed in Table I.

In the other 5 cases the preoperative diagnosis was not completely accurate. Four patients had an additional lesion that did not materially alter the course of treatment and 1 had an additional lesion that changed considerably the course of the operation. In no case was the diagnosis completely erroneous.

Comment

In the material reviewed a completely accurate preoperative diagnosis was made

in about 80 per cent of cases. Although the average complexity of the conditions to be diagnosed increased from Group 1 through Group 3, this accuracy of diagnosis was similar regardless of whether the diagnosis was established by clinical means alone (Group 1) when this was considered to be adequate by the clinician, by a combination of clinical means and catheterization (Group 2) when this was deemed to be advisable or by cardiac catheterization predominantly (Group 3) when a secure clinical diagnosis could not be made. Similar figures were obtained in the 162 cases in which catheterization was performed before referral to this clinic.

Of the 36 cases in which a lesion was found at operation in addition to lesions diagnosed in only 6 (17 per cent) (3 per cent of total) was the operative procedure considerably altered by the unsuspected finding. The incidence of such significant lesions for Groups 1, 2, and 3 was 3.8, 17, and 33 per cent respectively. The pertinent question is whether catheterization of each patient including those in Group 1 for whom a confident clinical diagnosis was made is justified in order to discover all or nearly all of the additional lesions present. Alternatively, could continual improvement in diagnostic acumen stimulated by review of diagnostic accuracy and pitfalls be relied on to achieve the same end? Indeed the key stone of correct diagnosis is the astute clinician. Data obtained at cardiac catheterization cannot be relied on exclusively in establishing consistently accurate diagnoses. The practice of performing cardiac catheterization on a routine basis for patients with congenital heart disease might tend to dull the acuity of the clinician.

This review indicates that the routine use of cardiac catheterization is not required for diagnostic purposes in all cases of congenital heart disease and that the additional expense, discomfort, and risk associated with this procedure should be reserved for selected cases of increased complexity or atypical nature. It should be obvious that a major function of studies by catheterization lies in clear definition of those cases unsuitable for cardiac surgery at the present time and that an assessment of this negative value if

such diagnostic studies is not defined by this report.

Summary

Since successful cardiac surgery depends to some degree on a correct preoperative diagnosis, a comparison was made of diagnoses based on clinical findings with those based on cardiac catheterization with respect to surgical diagnosis. The records of 196 patients operated on for congenital heart disease from July 1963 through June 1964 were reviewed for this purpose. A completely accurate diagnosis was made

in about 80 per cent of the cases, whether the diagnosis was made by clinical means alone, by a combination of clinical means and catheterization, or by catheterization alone. The use of cardiac catheterization was decided upon on the basis of certainty of clinical diagnosis. Of the cases in which unsuspected lesions were found at operation, the operative procedure was considerably altered by the unsuspected findings in only 6 cases (3 per cent of the total). It is suggested that routine cardiac catheterization in all cases of congenital heart disease is not required.

The Polarcardiograph Further studies of normal subjects, refinement of criteria for infarction, and a report on autopsied cases

Gordon E. Douer M.B.*

Heidi E. Horn

Vancouver, Canada

The usefulness of five simple criteria for the polarcardiographic diagnosis of myocardial infarction has been reported previously.¹ The evaluation was carried out on 493 patients of whom 227 were considered on the basis of electrocardiographic or postmortem evidence to have suffered infarction. In these the criteria gave the diagnosis in 94.7 per cent. On the other hand two independent readers using conventional electrocardiographic criteria reached the diagnosis from the single electrocardiogram (ECG) recorded when the polarcardiogram (PCG) was taken in only 66.1 per cent. In 11.6 per cent of the total population the PCC criteria indicated infarctions which could not be confirmed by available evidence. This figure provided an upper bound for the incidence of false positive diagnoses. A lower bound could not then be obtained because it would have required postmortem examination of all cases of false positive diagnoses.

A false positive diagnosis is probably more serious in a younger patient. An acceptable upper bound for the incidence of false positives would be 5 per cent.² It was decided therefore to study a group of normal young adults, males and females, and

to adjust the criteria to yield a false positive rate of less than 5 per cent. This paper describes the results of such a study, the modifications in the criteria that were required, and their effect on the incidence of correctly diagnosed cases when reapplied to the previous group. Their application to a subgroup of 78 autopsied cases is also described.

Method

Selection of cases. The definition of normal in a study of this type poses certain problems. It is not sufficient to take as normal those who have normal ECG's because we are trying to appraise a more sensitive test—cases of infarction correctly diagnosed on PCC evidence might be treated as normal cases on the basis of the ECG's. Similar objections can be raised with respect to any medical examination that is carried out in an attempt to define normality. Therefore it was decided to avoid a selection based on medical evidence. Since any hospital population tends to be selected on medical grounds, volunteers were obtained from a population found on the University campus.

Approximately 200 volunteers were stud-

From St. Anthony Hospital, and the Department of Pharmacology, University of British Columbia, Vancouver, British Columbia, Canada.

*Presently at the University of California, Los Angeles, California.

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Address reprint requests to Dr. Gordon E. Douer, St. Anthony Hospital, Vancouver, B.C., Canada.

ied. Because of obvious restraints on applying coercion to randomly selected individuals the possibility that the act of volunteering produced some degree of selection must be accepted.

Technical detail. The transistorized version of the foliaradiograph was used.² The x , y , and z orthogonal signals were obtained from a trunk-lead system.⁴ Subjects were studied in the supine position so the chest electrodes were applied at the level of the fourth intercostal space.⁵ As in previous studies the position of the C electrode was located with a chest protector. Buffer amplifiers were employed between the patient and the lead system network in order to avoid errors arising from unequal skin electrode resistances. The x , y , and z signals were recorded separately on 3 of the 4 channels of an FM tape recorder (PCC) and vectorcardiographic (VCC) readouts were derived from these recorded signals.

Recording the x , y , and z signals on magnetic tape allowed an innovation in clamping procedure.⁶ The signals were reproduced at slow speed in reverse direction and observed on an oscilloscope. A clamping triggering signal was injected onto the fourth channel of the tape recorder so that it fell during the $I-R$ interval. This signal was then used to activate the clamping circuits of the foliaradiograph during the final readout. Vectorcardiograms (VCCs) were obtained by means of a storage oscilloscope in which horizontal as well as vertical beam splitting was employed. This made it possible to display and photograph transverse frontal and sagittal loop simul- taneously.

Results

The terminology used in this paper is that described previously.²

The tracings of 3 of the 195 volunteers from a university population were rejected because of technical imperfections. There were 3 cases with abnormal ECGs but these were retained because of the requirement that medical ground should not affect selection (*ad nigrum*). The age and sex distributions of the sample are shown in Table I.

Normal values. The frequency distributions and upper and lower 25 percentiles

Table I Age distribution of sample studied

Age (y)	Males	Females
18-25	75	57
26-30	26	8
31-40	15	8
41 and older	3	1
Total	121	74

encompassing 95 per cent of the sample of 195 young adults are compared with corresponding distributions and percentiles derived from 192 males whose mean age was 38.6 years and who were selected on the basis of normal ECGs. Percentile points were calculated according to the method of Simonson.⁷

QRS duration. Unlike an ECG in which part of the QRS complex may be isoelectric in a given lead, the spatial magnitude curve of the PCC clearly indicates when all heart vectors are simultaneously zero and therefore provides a much clearer indication of the beginning and end of QRS. Furthermore, the paper speed used to record PCCs in the present study was 8 times faster than that generally used for ECGs, i.e., 20 cm per second.

The frequency distribution of the durations of spatial magnitude QRS complexes in the 195 young adults studied is shown in Fig. 1. Note that the distribution for females is slightly to the left of that for the total sample of young adults and corresponds with that for the 192 elderly men. The lower and upper percentiles for young adults are 64 and 104 msec compared with 61 and 103 msec for the elderly men (Table II).

I-R interval. The spatial magnitude curve of the PCC provides a convenient and accurate means of measuring this interval for reasons similar to those given above for QRS duration.

The frequency distributions and percentiles are given for the 195 young adults in Fig. 2 and Table II respectively. There appears to be no sex difference in the distribution. Note that there were 5 cases



Fig. 1 QRS interval determined from spatial magnitude tracings of 19 young adult females are shown by hatching. Previously reported intervals for 19 elderly men with normal electrocardiogram are shown by the dashed line.



Fig. 2 P-R interval in 19 young adult females are shown by hatching.

14-23 percent with $PR > 200$ msec; one of these had a P-R interval of 270 msec.

SPATIAL MAGNITUDE OF MAXIMUM QRS AND T VECTORS AND THE RATIO BETWEEN THEM The maximum QRS vector R and the maximum T vector T have spatial magnitudes VR and VT whose frequency distributions for the 19 young adults are shown in Figs. 3 and 4, and the ratio VT/VR in Fig. 5. There appears to be no marked sex difference in the VR distribution. In the distributions for females, males, and the 192 elderly males, there is a secondary peak to the right of the main peak. A similar observation seems to be valid for VT which in addition shows a slight sex difference. The distribution for females corresponds with that seen in the elderly males and lies slightly to the left of that seen for the young males. The lower and upper percentiles for the mixed population are somewhat above those obtained for the 192 elderly men (Table II). The same comment applies to the percentiles of the ratio VT/VR (Table II) which has the frequency distribution shown in Fig. 6 in which no marked sex or age difference is apparent.

SPATIAL ANGLE BETWEEN MAXIMUM QRS AND T VECTORS The angle between R and T has the distribution shown in Fig. 6. There is a slight sex difference; the distribution for males lying slightly to the right. The distribution covers a wide range; the lower and upper percentile points are situated at

Table III Comparison of 25th percentile points in two normal studies

	19 Elderly men with no mal ECG		19 young men and one female	
	Lower	Upper	Lower	Upper
P-R interval (msec)	—	—	11	18
QRS duration (msec)	81	105	66	104
VR (mV)	0.69	0.93	0.85	1.1
VT (mV)	0.19	0.4	0.2	0.46
VT/VR	0.14	0.60	0.18	0.69
$R-T$ angle (degrees)	19.2	147.6	1	106



Fig. 3 Magnitudes of maximum QRS vectors in same samples as in Fig. 1

15° and 110° (Table II) however a definite difference can be seen between the distribution for the 195 young adults and the 192 elderly males. The latter shows a secondary peak well to the right of the main distribution running the upper 21st percentile to 149° (Table II). This secondary peak probably indicates the inclusion of abnormal cases in the series. The angle between \bar{R} and \bar{T} is poorly indicated by the ECG so that abnormalities in this variable may be consistent with normal appearing ECGs.

DIRECTIONS OF QRS AND T VECTORS. The directions of \bar{R} in the 195 young adults are shown in Fig. 7. The distribution for the females is roughly concentric with that for the males but is less scattered. In a generalization for both sexes the distribution lies between latitudes 50° and 30° and between longitudes +10° and +90° with a few exceptions exceeding +90° and lying posterior to 30°. For the corresponding distribution found for 184 elderly males the reader is referred to the original article.⁸ That distribution was roughly similar. It was centered over the +30° meridian



Fig. 4 Magnitudes of maximum T vectors in same samples as in Fig. 1

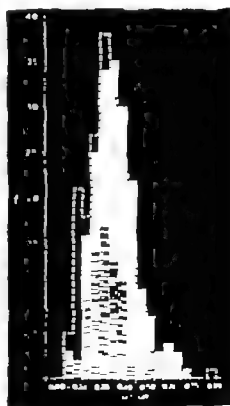


Fig. 5 Ratio of magnitudes of maximum T to maximum R in same samples as in Fig. 1



Fig. 6 Angle between maximum QRS and maximum T vectors in same samples as in Fig. 1

rather than the $+50^\circ$ meridian for the present series (Fig. 7). However it showed more scatter: there were 38 cases posterior to $+50^\circ$ as compared with 3 in Fig. 7. All but 10 cases 95 per cent lie in an area one twelfth that of the globe.

In some cases \bar{R} is ambiguous because of two peaks of equal height in the spatial magnitude tracing. For this reason the vector \bar{IR} has been proposed. It is defined as the vector occurring at the instant at which the area beneath the QRS complex in the spatial magnitude tracing is half of its final value. This is readily obtained from the simultaneously recorded integral of the spatial magnitude tracing. The directions of \bar{IR} are shown in Fig. 8. The distribution is very similar to that for \bar{R} . This suggests that the direction of \bar{IR} may be substituted for that of \bar{R} when the latter is ambiguous. Note that even though \bar{R} may be ambiguous \bar{IR} the magnitude of \bar{R} is not hence it is not necessary to substitute the magnitude of \bar{IR} for \bar{IR} .

The directions of \bar{T} in the 195 young adults are shown in Fig. 9. The center of the distribution for females is about 20° degrees posterior to the center of the distribution for males but there is considerable overlap between the two distributions.

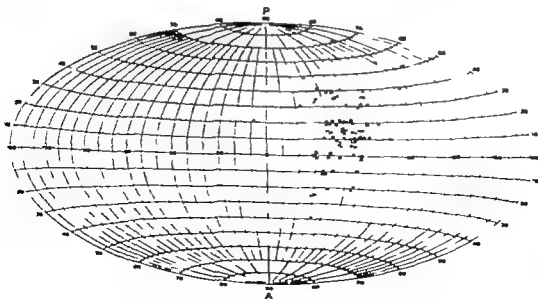


Fig. 7 Directions of \bar{R} in 195 young adults: stars indicate females

butions. The distribution for both sexes shows much less scatter than that noted for R and all but 6 cases 97 per cent lie in an area one nineteenth that of the sphere. With 3 exceptions the distribution is bounded by longitudes $+10\alpha$ and $+60\alpha$ and latitudes $10A$ and $65A$. The case with the T direction on the 180 degree meridian close to the anterior pole had an abnormal ECG. The distribution of T found for the 192 elderly males was approximately concentric with the above mentioned distribution but showed more scatter. 95 per cent were contained in one fifteenth of the global surface.¹ Thus the scatter for the young adults for T directions is 0.8 of that for the elderly men.

Criteria for infarction

Application of criteria to 195 young adults—refinements. The PCC criteria for infarction previously reported are given in Fig. 10.¹ When these criteria were applied to the 195 young adults it was found that downslopes occurring early in the transverse and sagittal longitude tracings of the QRS vectors (β_{QRS} and γ_{QRS}) were common. However at the end of the initial β_{QRS} downslopes it was noted that β_{QRS}

exceeded $+75$ in all but 9 cases. Initial γ_{QRS} downslopes occurred within the first 8 msec. after the onset of the QRS complex in the spiral magnitude curve (Δ_{QRS}) in all but 7 cases. These findings suggested refining the criteria indicated in the right hand column of Fig. 10. The refinement that a Q wave should appear in the γ lead as a necessary condition for the diagnosis of inferior infarction is actually a consequence of the previous definition and not therefore a new condition; however it is sometimes easier to apply in practice than $\gamma_{QRS} > -175$. Note that the Q wave may be of any size. If it is so small as to be equivocal the diagnosis would be doubtful or negative for inferior infarction. Fig. 11 illustrates β_{QRS} and γ_{QRS} downslopes which would not yield diagnoses of infarctions because of the above mentioned refinements.

Application of the refined criteria to the 195 young adults gave the following result: positives 6 (3.08 per cent) and doubtfuls 4 (2.05 per cent).

*Application of refined criteria to 493 cases previously reported.*¹ The results of applying the refined criteria for infarction to the series of 493 cases previously studied are

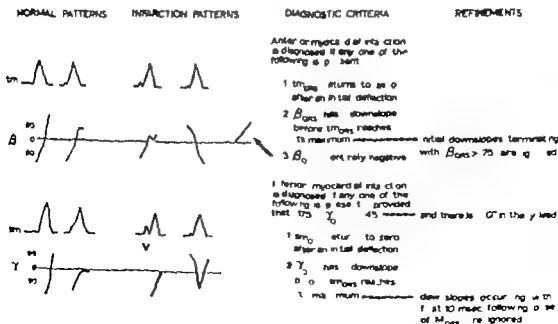


Fig. 10. The polarcardiographic criteria for infarction with refinements.

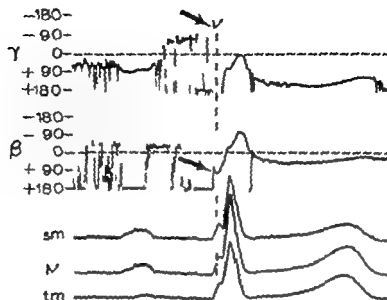


Fig. 11 The fit of the refinements in Fig. 10 negates a diagnosis of AMI (initial downslope terminates with $\Delta_{QRS} > +75$ and of AMI γ_{QRS} has a downslope which falls within first 10 msec (indicated by vertical dashed line) after onset of Q_{γ} .

shown in Tables III, IV, and V. The figures in parentheses were obtained using the original criteria. Additional evidence, generally postmortem, has been acquired and applied to the current figures. One FCC diagnosis (FCC Δ) previously treated

Table III Diagnosis of myocardial infarction (out of 493 cases). Polarcardiographic diagnosis (PCG Δ) vs diagnosis from single ECG (ECG Δ) and from all ECGs and postmortem data (Best Δ) (where relevant)

	PCG Δ +	PCG Δ -	PCG Δ
ECG Δ +	143 (146)	6 (3)	1 (1)
"	5 (9)	191 (173)	4 (7)
"	51 (56)	17 (14)	2 (1)
	69 (791)	217 (190)	7 (9)
BEST Δ +	206 (213)	23 (10)	3 (2)
"	44 (51)	185 (174)	4 (7)
"	19 (22)	(6)	0 (0)
	269 (291)	21 (190)	7 (9)

Figures in parentheses are those previously reported, emphasis is original criteria.

as doubtful should have been negative. This has been corrected in the tables; the PCC Δ is the diagnosis obtained employing the refined criteria. The FCC Δ is a composite based on the independent diagnoses of two skilled interpreters who saw separately the ECG taken at the time the PCC was recorded, but who were given no other information. The Best Δ was based on all ECG and autopsy evidence available in those cases in which there was a conflict between the FCC Δ and the PCC Δ . In the absence of significant information or when they did not conflict, the FCC Δ and the Best Δ were the same.

In the 493 cases the PCC Δ was positive for infarction on the basis of the refined criteria in 269, negative in 217, and ambiguous in 7. The ambiguities derived from very small abnormalities associated with muscle tremor. Of the 269 cases in which the PCC Δ was positive, the ECG Δ was positive in only 143, but when more information was provided about many of these cases, agreement with the PCC Δ improved; the Best Δ was positive for 206 cases. Thus there was a trend toward the PCC Δ of 63 cases. When the PCC Δ was negative, there were only 6 cases in which the FCC Δ was positive. No distinction between subendo-

Table IV Result of combining + and - diagnoses for myocardial infarction in PCGΔ ECGΔ and BestΔ out of 493 cases

PCGΔ agreement (as to occurrence or non-occurrence of infarction)	With ECGΔ (cases)	With BestΔ (cases)
Complete as to location of infarction	96 (93)	144 (162)
Not complete as to location	45 (53)	58 (53)
As to occurrence of infarction	141 (146)	202 (215)
As to nonoccurrence of infarction	190 (173)	187 (174)
Total agreement	331 (319) 67.2% (64.7%)	384 (389) 78.0% (78.9%)

Figure in parentheses shows the corresponding number in the group of criteria

Table V Incidence of false positives in PCGΔ based on various yardsticks

	In series of 493 cases		In 78 infarctives	In 195 young adults
	Based on ECGΔ	Based on BestΔ	Based on P V findings	Based on assumption of normality
Incidence of false positive in PCGΔ (per cent)	14.6	8.5	6.4	3.1

cardial and transmural infarction is made in Table III there were 21 cases in which the ECGΔ was subendocardial infarction i.e. the diagnosis was not based on the QRS complex. Although the PCG criteria so far relate only to the QRS complex the diagnosis of infarction was made in 16 of these cases. There were only 7 cases in which the PCGΔ was doubtful whereas there were 70 cases in which the ECGΔ was doubtful—a figure which was reduced to 76 in the BestΔ. Comparison with the earlier figures shows that there are now only 9 fewer cases with both the BestΔ and the PCGΔ positive. Additional information has added 7 cases to the total number with the BestΔ positive.

In some cases a diagnosis of both anterior infarction (AMI) and inferior infarction (IMI) was made on the basis of the refined ICC criteria whereas the ECGΔ or the BestΔ indicated either one

of these and vice versa. Agreement as to location was considered to be partial in these cases. There was complete agreement as to location of the infarct in 96 cases with the ECGΔ and in 144 cases with the BestΔ (Table IV). The PCGΔ differed as to location of the infarct from the ECGΔ in 45 and from the BestΔ in 58 cases. Agreement as to whether or not infarction had occurred existed in 331 cases (67.2 per cent) with the ECGΔ and in 384 cases (78.0 per cent) with the BestΔ. These figures are not greatly different from those previously obtained with the unrefined criteria (Table IV in parentheses).

As already indicated the object in refining the criteria for infarction was to guard against an excessive number of false positives especially in young adults. In the 493 cases the incidence of apparent false positives based on various yardsticks is shown in Table V. On the basis of the

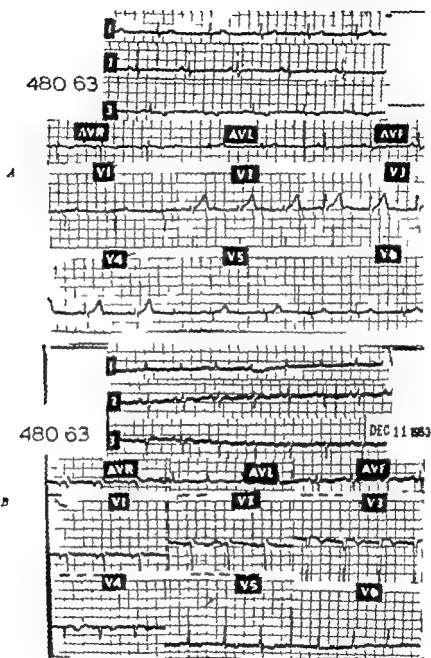


Fig. 17. Changes secondary to subacute bacterial endocarditis. A. Six months before death. B. One month before death.

FCC 3 it is 15.6 per cent but when more information is provided as in the Best 3 it reduces to 8.7 per cent. This would still be too high were it not for the expectation that further information would reduce it.

In summary, in the group of 493 cases on the basis of all FCC and I M evidence available the diagnosis of infarction was

made in 234 cases. In these cases the diagnosis based on the FCC alone was infarction in 110 or 64 per cent. In the same cases the diagnosis based on the PCC alone employing the refined criteria was infarction in 206 or 85 per cent.

Application of refined criteria to 75 atypical cases (Out of the 493 cases referred

to these autopsies were obtained in 76 and the hearts in 61 were examined by at least one of the authors. The importance of being present when autopsy examination of the heart is carried out should be stressed. This does not imply criticism of the pathologists but merely the fact that one tends to discover something more readily if one is looking for it. All too frequently the postmortem report supported by a cursory pathologic examination is erroneously considered to be the final verdict.⁴

Of the 78 autopsied cases infarcts were found at autopsy in 38. The ECGA was positive in only 23 or 40 per cent of these whereas the PCCA was positive in 46 or 79 per cent.

There were 6 cases in which the PCGA was positive but no infarcts were found at autopsy. It is most unfortunate that the hearts in 4 of these cases were not available to the authors and were not bread loafed.⁷ Death in 1 of these cases was due to subacute bacterial endocarditis and autopsy showed multiple small areas of myocardial fiber replacement by granulation tissue. Before death ECGs showed typical changes of infarction (Fig. 12). From an electrical standpoint the lesions seen were equivalent to infarcts so that this case should not fairly be considered to be a false positive. Thus there were 5 false positives for the PCGA or 6.4 per cent (Table V). However in one of these the previous LCGs were strongly suggestive of anterior infarction, the patient had had typical attacks of angina and had been considered to have a typical infarction on clinical grounds. The heart weighed 530 grams; it was not bread loafed and it may be that a significant infarction was missed at autopsy in this case. If true the false positive rate was 5.1 per cent.

Discussion

The normal study reported here is of interest not only because it furnishes a definition of normal that is statistically acceptable but also because it provides a basis for comparison between samples of almost equal size from two different populations—a mixed population of young presumably healthy adults and a population of elderly males who had normal

ECGs. The rather small differences between the percentile PCC data and angular plots obtained from the two samples despite a rather wide discrepancy in age suggests that the variables studied tend to be rather stable with age. This is satisfactory because it means that age factors may not need to be taken into account in PCC interpretations applied to adult populations. Furthermore although a slight sex difference was noted in some distributions in the present series the difference would probably be small enough to be neglected for most purposes. The fact that different instruments were used in the two studies and that these employed radically different components and had different readouts calibration procedures and paper speeds yet gave results that were remarkably close speaks well for the accuracy of the technique.

Distributions for QRS and T latitudes and longitudes employing a longitudinal polar axis for 173 normal men have been reported recently by Bewick, Jordan and Kilpatrick.⁸ However the directions they gave were obtained by employing the areas of the QRS complex and the T wave in the x-y and z orthogonal leads as x-y and z coordinates to define QRS and T vectors respectively. These vectors do not correspond with R and T.

As stated in the introduction the reason for this normal study was to ensure that the incidence of false positives was not excessively high. Table V presents various estimates of this incidence. In the 493 cases if the ECGA is taken as a yardstick the incidence of false positives is 14.6 per cent. If this figure were very much lower there would be little to be gained from the use of the PCC because it would indicate that if the PCCA was positive then the ECGA would be positive too. When all the ECG and autopsy evidence available is taken into consideration the false positive rate falls to 8 per cent. However the evidence in this series of 493 cases is not complete and it might well be that more evidence would reduce this rate further. In the 78 autopsies in which the evidence was complete the rate fell to 6.4 per cent for the 193 young adults; the rate was 3.1 per cent.

The modified diagnostic criteria for

myocardial infarction may thus be employed with confidence that the odds against any given positive PCC Δ being wrong are 20:1.

Summary

A population sample of 197 young men and women has been studied in order to define normal values for polarcardiographic diagnosis and to refine five simple criteria for infarction to yield an incidence of false positives of less than 3 per cent. The incidence became positive 3 per cent, doubtful 2 per cent. The criteria were reapplied to a group of 493 patients who had been studied previously and to 78 autopsied cases which formed a subgroup. In the 493 patients there were 234 who were considered to have suffered infarction. In these the refined criteria give the diagnosis in 88 per cent. On the other hand two independent readers using conventional criteria reached the diagnosis from the single ECG recorded at the same time as the PCC in only 64 per cent. In the 78 autopsied cases there were 36 with infarcts. The ECG gave the diagnosis in 40 per cent of these whereas the PCC gave the diagnosis in 9 per cent.

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A simplified method for calculating the pulmonary valvular area

James H. Moller, M.D.

Paul Adams, Jr., M.D.

Minneapolis, Minn.

The selection of patients with isolated pulmonary valvular stenosis for operation is commonly made on the basis of the level of right ventricular systolic pressure. The severity of the pulmonary stenosis can be more accurately assessed when both the right ventricular pressure and the cardiac output are considered. In 1951 Gorlin and co-workers^{1,2} presented formulae for pulmonary valvular area and pulmonary valvular resistance. These formulae consider various relationships between the right ventricular pressure and the cardiac output.

The determination of the pulmonary valvular area yields information which is easily understood by the clinician and surgeon evaluating a patient with pulmonary stenosis. The formula for pulmonary valvular area is probably not more widely applied because of several time consuming steps necessary in performing the calculation from the pressure tracings recorded at catheterization.

The purpose of this communication is to present a simplified method of determining the pulmonary valvular area which eliminates the necessity of measuring various factors of the pressure contour. This method is based on data obtained at cardiac catheterization in children with isolated pulmonary valvular stenosis and by the

application of the formulae of Gorlin¹ to the analysis of this data.

Source of data

In 108 children with isolated pulmonary valvular stenosis studied in the cardiovascular laboratory at the University of Minnesota Hospitals pressure tracings recorded at cardiac catheterization were adequate for this analysis. In 40 of the 108 cases oxygen consumption was determined by the Tread Scholander method so that by applying the Fick principle the cardiac output could be calculated utilizing the simultaneously measured arteriovenous difference in oxygen content.

Pulmonary valvular area and the pulmonary valvular resistance were calculated in each of these 40 cases utilizing the following formulae of Gorlin^{1,2}:

$$PVA (cm^2) = \frac{\text{systolic flow}}{\text{closure through a/e}}$$

$$PVA = \frac{\frac{CO \times 1,000}{SEP \times HR}}{44.5 \sqrt{RV_m - PA_m}}$$

$$PVR (\text{dynes sec. -cm.}^{-2}) = \frac{\text{pressure gradient}}{\text{flow}}$$

$$PVR = \frac{RV_m - PA_m \times 1.332 \times 60}{CO}$$

F is the Department of Pediatrics, University of Minnesota, Minneapolis, Minn.

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PVA = pulmonary valvular area PVR = pulmonary valvular resistance CO = cardiac output RV_m = mean right ventricular systolic ejection pressure PA_m = mean pulmonary arterial pressure SEP = systolic ejection period and HR = heart rate

To determine the mean right ventricular systolic ejection pressure the right ventricular pressure contour was analyzed and perpendiculars were dropped to the zero line of the recording from the point in systole at which the right ventricular pressure first exceeded the pulmonary arterial pressure and from the diastolic notch. The interval between these two perpendiculars is the systolic ejection period i.e. the period when the pulmonary valve is open. The area under the right ventricular pressure curve between the perpendiculars was measured by a planimeter and divided by the distance between the perpendiculars to find the mean right ventricular systolic ejection pressure. In each instance duplicate or triplicate measurements were made of each of four ventricular complexes.

The mean pulmonary arterial pressure was used instead of the mean pulmonary arterial systolic ejection pressure. This assumption introduced only a small error in the calculations since the values are nearly identical.

Observations

If the formulae for pulmonary valvular area and for pulmonary valvular resistance the latter requires the least number of steps in its calculation. If a constant relationship existed between these formulae by calculating the pulmonary valvular resistance one could determine pulmonary valvular area. In the formula for pulmonary valvular resistance however the value for the mean right ventricular systolic ejection pressure is required in the calculation.

Our initial step was to determine whether a direct relationship existed between the right ventricular systolic pressure and the mean right ventricular systolic ejection pressure. In 108 cases the values for the right ventricular systolic pressure measured at the time of catheterization were compared to the values of the mean right ventricular systolic ejection pressure de-

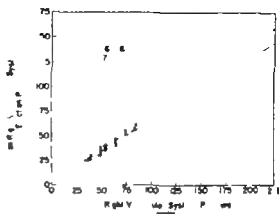


Fig. 1 Relationship between right ventricular systolic pressure and mean right ventricular systolic ejection pressure in 108 children

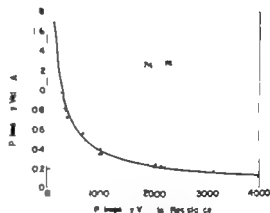


Fig. 2 Relationship between pulmonary valvular area (cm²) and pulmonary valvular resistance (dynes/cm²) in 40 children with increased cardiac output

termined by the method outlined above. There is a linear relationship between these two measurements of pressure (Fig. 1). The mean right ventricular systolic ejection pressure is equal to 0.66 peak right ventricular systolic pressure ($y = 3.16 + .63x$, $r = .97$). This ratio of 0.66 is similar to that found by other workers.¹¹ Since a linear relationship exists between these two factors one can estimate the mean right ventricular systolic ejection pressure by knowing the peak right ventricular systolic pressure. The necessity of making measurements from the right ventricular pressure contours is thereby eliminated and this factor may be used to calculate the pulmonary valvular resistance.

In Fig 2 the pulmonary valvular area calculated by Gorlin's method has been related to the pulmonary valvular resistance in the 40 patients in whom the cardiac output was measured. The values are clustered along the curve ($y = 74e^{-0.001x}$). By knowing the pulmonary valvular resistance therefore one can estimate a corresponding pulmonary valvular area.

Conclusions

To determine the pulmonary valvular area the formula for pulmonary valvular resistance is utilized:

$$PVR = \frac{RV_m - PA_m}{CO} \times \frac{1.332 \times 60}{1000}$$

A substitution of 0.66 peak right ventricular systolic pressure is made for the mean right ventricular systolic ejection pressure and the pulmonary valvular resistance is calculated:

$$PVR = \frac{0.66 RV - 1A}{CO} \times 80$$

This value for resistance is located on the abscissa of Fig 2 and the corresponding pulmonary valvular area is found on the ordinate.

Summary

In order to accurately assess the severity of pulmonary valvular stenosis one must

consider both the right ventricular systolic pressure and the cardiac output. The calculation for the pulmonary valvular area utilizes both of these factors but has been time consuming to perform. A simplified method is presented for determining the pulmonary valvular area by calculating the pulmonary valvular resistance and relating this value to the pulmonary valvular area.

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Ectopia lentis, cardiology, and "the sign of the tremulous iris"

John H. Stone M.D.*

Atlanta Ga

Ectopia lentis or displacement of the lens of the eye is a finding that in many ways is as important to the cardiologist as to the ophthalmologist. The purpose of this communication is summarized as follows: (1) to review the pertinent pathologic anatomy, (2) to outline the disease entities in which displacement of the lens occurs, and (3) to underscore a physical finding which is familiar to the ophthalmologist but which I believe is often not utilized fully by the internist or cardiologist.

Pathologic anatomy

If the suspensory ligaments which fix the lens in place are defective (see Fig. 1) the lens loses some of its support and may assume any of a number of positions. If rupture of the ligaments is not extensive the lens remains in the pupillary aperture and is said to be *subluxated*. When subluxation alone is present a number of optical events ensue. Because the lens is displaced from the center of the pupil light is bent through the more highly refractile periphery of the lens and a lenticular myopia is usually produced.¹ The patient himself may note diplopia since part of the light passing through the pupil is refracted by the subluxated lens and part is not thus two images are formed on the retina. Astigmatism may occur if the lens is tilted on its axis.

If the ligaments are extensively rup-

tured the lens moves out of the pupillary opening and is said to be *dislocated*. Under those circumstances it may move into either the anterior chamber or posteriorly into the vitreous (in the latter case coming to lie finally against the retina). Secondary glaucoma is very likely to occur with displacement anteriorly. Posterior displacement is better tolerated but complications including glaucoma usually ensue eventually.¹

Associated diseases

Ectopia lentis has been noted in several disease entities, including some of those designated as heritable disorders of connective tissue.² These and other processes (see Table I) will now be reviewed.

Of the disease processes in which ectopia lentis is present Marfan's syndrome stands foremost. Indeed this ocular finding is one of the salient characteristics of this disorder. Other major signs may be found in the skeletal and cardiovascular systems. Arachnodactyly, kyphoscoliosis, pectus deformities, and hyperextensible joints are frequent skeletal abnormalities. Cardiovascular pathology is an important cause of death and includes aortic or pulmonary artery aneurysmal dilatation and/or dissection, accumulation of the aortic cusps,³ and mitral insufficiency.⁴ Congenital heart lesions have also been seen with Marfan's syndrome but their relationship to the primary connective tissue disorder is un-

Table 1 Conditions in which ectopia lentis may occur

- 1 Marfan syndrome
- 2 Homocystinuria
- 3 Brachydactyly (Weill Marchesani) syndrome
- 4 Ehlers Danlos syndrome
- 5 Osteogenesis imperfecta
- 6 Ocular trauma
- 7 Spontaneous

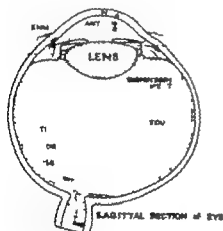


Fig. 1 Normal anatomy of the eye

clear.² McKusick⁴ estimates that perhaps 70 per cent of patients with ectopia lentis will have stigmata of Marfan's syndrome; conversely, about 80 per cent of patients with Marfan's syndrome have ectopia lentis. In this regard it is of interest that in his original case report of a man with long slender extremities and dolichocephaly Marfan stated specifically that the eyes were normal.⁵ The subluxation in this entity is usually superior and bilateral.⁶

In 1963⁷ a new inborn error of amino acid metabolism was recognized. This syndrome called homocystinuria closely mimics Marfan's syndrome including ectopia lentis and similar skeletal abnormalities.⁸ Ectopia lentis has been found in the great majority if not all of patients with homocystinuria and as in Marfan's syndrome myopia, retinal detachment and glaucoma may also occur. Cardiovascular problems

mainly arterial and venous thromboses are often present. Aortic regurgitation seen frequently with Marfan's syndrome has not yet been observed in homocystinuria.⁹

Ocular abnormalities including ectopia lentis, spherophakia, microphakia and glaucoma are major features of the brachydactyly or Weill Marchesani syndrome. The other physical findings in this entity—short stubby fingers, small stature and mental retardation—stand in sharp contrast to those in Marfan's syndrome.¹⁰ However, one family which contained over thirty examples of Marfan's syndrome also had two members with features suggestive of the brachydactyly syndrome. This led the author to suggest that the two disease processes may overlap or indeed be genetically the same.¹¹ No specific cardiovascular findings have to my knowledge been described.

Ectopia lentis has been noted at least once in both the Ehlers-Danlos syndrome¹² and osteogenesis imperfecta¹³ as recorded by McKusick. The Ehlers-Danlos syndrome characterized by hyperelasticity of the skin and hyperextensibility of the joints is most significant to the cardiologist because of the occasional dissecting aneurysm. In general though cardiovascular pathology is notably lacking. A case of Ehlers-Danlos syndrome with a minus of Valsalva aneurysm and aortic insufficiency has been reported.¹⁴ A recent report of a case with bifidity of the pulmonary artery and anomaly of the aortic arch (abnormal course of aorta and tortuous efferent vessels) has appeared.¹⁵

Another recent paper¹⁶ indicates that patients with osteogenesis imperfecta may also have significant associated heart disease. Of the 3 patients whose cases were included in the above report two had aortic insufficiency secondary to dilatation of the aortic root without apparent cause; the third patient had lesions of the pulmonary, aortic and mitral valves and microscopic changes of cystic medial necrosis were present in the pulmonary artery and aorta.

Dislocation of the lens occurs most frequently on a traumatic basis. It apparently may also occur spontaneously in middle aged or older individuals in cases in which the lens is particularly weak.

Examination for ectopia lentis

A complete ophthalmologic examination for ectopia lentis including use of the slit lamp may reveal minor but important changes in the suspensory ligaments. This sophisticated examination however although highly desirable in some cases may not be necessary in many others if an informed physical examination is done. As can be appreciated from the accompanying figure, a subluxated lens may be seen with the ophthalmoscope: the curved edge of the lens appearing as a dark line in the pupillary aperture.¹ However the pupil is almost always small and difficult to dilate (especially in Marfan's syndrome) and this may preclude or render ophthalmoscopic examination difficult if best.

The tremulous iris

An even simpler diagnostic maneuver is used by ophthalmologists. Because the lens is subluxated the inferiorly placed iris loses some of its support and fluttering of the iris occurs.⁴ As the patient moves his eyes from side to side the iris is noted to tremble either in part or as a whole. This sign is known as *iridodonsis*. That the ophthalmologist finds this a useful sign is attested to by the fact that Lutman and Neel¹⁶ mention iridodonsis as a positive finding in the great majority of their cases of Marfan's syndrome. I have recently observed several patients with Marfan's syndrome who exhibited iridodonsis to a striking degree. Subsequent conversation with some of my medical colleagues concerning these patients prompted me to delve further into the subject and to write this report.

The only other major circumstance in which iridodonsis may occur is after cataract extraction as would be expected from the foregoing discussion.

It is my impression that the clinical usefulness and use of application of the sign of the tremulous iris has not been fully appreciated by cardiologists and internists especially. Whereas some cases of ectopia lentis may not exhibit this sign when it is present it appears to be a sure sign of subluxation of the lens.¹ As such it may prove to be useful in the continuing correlation

of physical findings with the pathologic anatomy of disease.

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Myocardopathy in Chagas' disease

1 Comparative study of pathologic findings in chronic human and experimental Chagas' myocarditis

Alfonso Anselmi M.D.*

Felre Pifano C. M.D.*

Jose Angel Suarez M.D.**

Orlando Guardia M.D.

Caracas, Venezuela

Great emphasis has been placed in the past on the importance of scattered fibrotic plaques found in heart musculature preventing chronic inflammation due to *Schizotrypanum cruzi* (*S. cruzi*).

Diaz and associates¹ have stressed the presence of thinning of several regions in the free ventricular walls and Laranja and associates² have found marked thinning of the left ventricular apex in 3 necropsy cases. These changes have been attributed by other authors³⁻⁵ to confluent fibrotic processes predominating at the apex producing at times aneurysm like dilations of the affected ventricular wall.⁶⁻⁸

Mora⁹ was the first to describe thinning of the free ventricular wall and the formation of aneurysms in a case of Chagas' myocarditis at a site other than that classically described. Frequent discrepancies have arisen also in regard to the pathogenetic mechanism responsible for the degenerative changes observed in muscular fibers and replacement of them by collagen fibers. It has been suggested that the cru-

sive factors of the histologic changes produced by *S. cruzi* are mechanical destruction of fibers by the parasite^{1,10,11} toxic^{12,14} or immunologic mechanisms^{11,15} neuro-genetic factors,¹⁶ vascular factors,¹⁷ and atrophy of the fibers due to hypertrophy of the interstitial space.^{18,19}

In the present study an analysis is made of the pathologic findings in dogs with chronic experimental *S. cruzi* infection. These findings are compared with those in human autopsy material from the Institute of Pathology of the Universidad Central de Venezuela. Finally an attempt is made to study the changes produced in the electrocardiogram by the areas of fibrosis in experimental Chagas' myocarditis and in the anatomic electrocardiographic correlations in human beings.

Material and method

Twenty nine hearts from patients showing a chronic inflammatory process at autopsy were studied histologically. The findings obtained were correlated with corre-

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*Instituto de Patología, Universidad Central de Venezuela, Caracas.
**Instituto de Patología, Universidad Central de Venezuela, Caracas.
Address correspondence to Alfonso Anselmi, Instituto de Patología, Universidad Central de Venezuela, Caracas.
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sponding electrocardiographic changes. The selection of cases was based on clinical and pathologic data. At this point we should like to add that autopsies 1 to A 2503 were performed without following specific criteria. Although our impression is that there were some cases of chagasic myocarditis among them, the correct diagnosis was not confirmed except in Cases A 826, A 1217, A 1131, A 2199, and A 2503. Clinically, the cases selected for study were those which had a suggestive epidemiologic background, a positive complement fixation reaction (CFR) for *S. cruzi*, and clinical and electrocardiographic evidence compatible with that observed in chronic Chagas myocarditis. From the pathologic point of view, the cases were selected on the basis of macroscopic flaccidity of the myocardium and dilatation of the chambers with or without mural thrombus. Microscopically, all these cases had a focal or diffuse inflammatory reaction in the free ventricular and atrial walls of the heart and an absence of inflammatory reaction in other organs.

A correlation between pathologic and electrocardiographic findings was made in experimental animals. Techniques of infection in dogs, the evaluation of myocardial damage, and the tracing methods employed have been described previously.^{10,11} An absence of atherosclerotic coronary lesions was observed in all of the cases studied.

Preparation of the hearts was as follows: the heart was separated from the structures to which it was attached and was removed from the thoracic cavity. Care was taken to obtain sufficiently long pulmonary and caval veins. After initial washing, 10 per cent formalin was injected into the left and right chambers. The left chamber was injected via a pulmonary vein with ligatures placed on the other pulmonary vein and the aorta, and the right chamber was injected via a superior vena cava with previous ligation of the inferior vena cava and the pulmonary artery. Injection pressure was 50 ml. of water. The heart was then submerged in 10 per cent formalin for 5 days so that it would retain its natural shape and size.

Sections perpendicular to the longitudinal axis from apex to base were made at 5 mm. intervals. For histopathologic study

blocks were taken from the anterior lateral and posterior surfaces of the left ventricle and from the anterior and posterior surfaces and edge of the right ventricle. Superior middle and inferior areas of these were selected for sectioning. Blocks from the middle superior and apical areas of the interventricular septum were also taken.

Areas of intense and generalized fibrosis and their surroundings and areas with thinning of the ventricular wall were included in those blocks in order to analyze the affected regions plus the ones around them. Sections were stained with hematoxylin-eosin, Gomori, and Van Gieson stains.

An important reduction in thickness was taken as the criterion of thinning of the free ventricular wall together with normal thickness in the neighboring areas. In the right ventricle with normally thin walls the criterion for decreased thickness was translucency of a given area.

Results

I. Gross anatomy. Hearts from patients with chronic myocardopathy of chagasic origin present a macroscopic increase in total volume due to dilatation of the chambers. The degree of dilatation was significant and was present in all chambers in most of the cases studied. Table 1 shows the degree of dilatation on a scale of 1 to IV in each case. Only 3 cases (A 2769, A 3057, and A 3293) showed scant dilatation but this was in conjunction with hearts of smaller size.

An important reduction in the thickness of the free ventricular wall was found in the majority of cases. Few hearts had walls of normal thickness for the reason that hypertrophy of the heart was related to weight which varied from 260 to 795 grams.

In experimental cases chronic Chagas infection (with a duration longer than 1 year and frequent reinfections) produces significant dilatation of all chambers although the right ventricle is found to be affected more frequently. Fig. 9 shows the results of a 5 year infection in a dog: there is dilatation of all chambers with a significant decrease in the thickness of the free left ventricular wall and thinning and fibrosis of the free right ventricular wall.

Table 1 Postmortem findings in 29 human cases

Autopsy number	Dilatation							Thrombosis					Heart weight (Gm)
	Age (yr)	Sex	LA	RA	LV	RV	RVOT	RA	LA+p	RIA+p	LV	RV	
A 826	26	F	III	IV	IV	IV	IV			+	+	+	630
A 1217	48	M	III	III	III	IV	III				+		685
A 1781	31	M	III	IV	IV	IV	III			+	+	+	600
A 2199	50	F	II	III	III	III	III			+	+		520
A 2503	66	F		I	I	II	I				+		316
A 2721	36	F	II	II	III	II	I				+		480
A 2769	49	F			I	I							260
A 2930	15	F	I	I	III	II	III			+	+		453
A 2952	64	M	II	II	II	I	II			+			498
A 2954	44	F	I	II	II	II	III						490
A 2971	40	M	II	III	II	III	III			+	+	+	436
A 2981	40	M	III	III	IV	IV	IV			+	+	+	424
A 2984	66	M	II	III	III	II	III	+		+	+		464
A 3051	22	F		I	I	I	II						273
A 3093	68	F	II	III	II	II	II		+	+			502
A 3096	32	M	II	II	II	III	III			+	+		414
A 3116	18	F	II	III	II	III	III						400
A 3177	66	F	II	III	II	II	III					+	370
A 3183	32	F	III	III	III	III	III						665
A 3185	38	M	III	IV	IV	III	IV			+			498
A 3197	34	M		I	II	II	II			+			434
A 3199	64	F	II	III	II	III	II			+			370
A 3247	54	M	I	III	III	II	II						510
A 3280	45	F	I	II	II	II	II			+	+	+	300
A 3283	66	M	II	III	III	III	III				+	+	537
A 3286	M	M	III	IV	IV	IV	IV			+	+		785
A 3293	48	M				I	I				+	+	290
A 3320	55	M	II	III	II	III	III			+	+		670
A 3362	45	M	III	III	II	III	III			+			487

LA Left atrium RA Right atrium LV Left ventricle RV Right ventricle RVOT Right ventricular outflow tract LA+p Left atrial appendage RA+p Right atrial appendage

Table 11 Type and distribution of lesions in human cases (postmortem study)

Single lesion (3 cases)	3 cases with fibrosis and thinning at LV apex 1 case with fibrosis and thinning at the superior aspect of the RV posterior wall 1 case with fibrosis and thinning at the superior aspect of the posterior wall of the LV
Multiple lesions	6 cases LV apex—Posterior wall LV 1 case LV apex—Lateral wall LV (high) 1 case LV apex—Anterior and lateral wall LV 1 case LV apex—Anterior and lateral wall LV Posterior wall RV 1 case LV apex—Posterior wall LV—Middle intra-ventricular septum 1 case LV and RV apex—Anterior wall LV 2 cases LV and RV apex—Posterior wall LV 1 case LV and RV apex—Lateral and posterior wall of LV 1 case LV and RV apex—Posterior wall LV Posteroanterior intra-ventricular septum 1 case RA—Posterior and anterior walls RV

Both the human and canine hearts showed significant muscular friability: the organs were easily depressed under pressure and showed creases when placed over a hard surface.

Of the 29 human cases studied 21 presented the previously described anomalies. 8 did not show thinning or extensive fibrosis in the cardiac walls. Of the 21 pathological cases 5 showed a single lesion (fibrosis and thinning of the right or left free ventricular wall) and 16 showed multiple lesions (fibrosis and thinning in several zones of the heart). The distribution of the anomalies is shown in Table II. The lesions found were of an irregular round shape and they varied in size from 1 to 4 cm.

Fig. 1 (A 3185) shows the typical ventricular dilatation with thinning of the ventricular wall in the anterior and posterior regions. The lateral wall shows a semicircular fibrotic zone extending from the antero-lateral surface to the posterior surface and small foci of fibrous tissue in the subendocardium. The translucent zone at the apex of the left ventricle is due to an extensive area of fibrosis which produced a foliaceous thinning at that level.

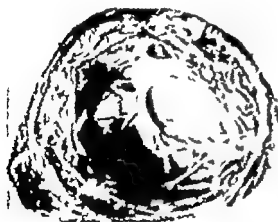


Fig. 1 Transverse section at the level of the inferior half of a heart (A 3185) with chronic myocarditis of 5 cm origin. Marked dilatation of the LV of 5 cm with an increase in trabeculation and significant thinning of the wall. Heart weight = 498 grams. There is an extensive and dense fibrotic plaque at the lateral aspect of the wall and smaller fibrous plaques dispersed through the muscular wall. The apex of the LV translucent as a result of thinning of the foliaceous type connective tissue.



Fig. 2 Aneurysmal dilatation 4 by 3 cm located at the posterolateral zone of the LV wall immediately below the AV valve. As seen from the interior of the LV chamber the wall is translucent in the subvalvular mitral area. Wall thickness was 1 mm and consisted of a fibrous plaque. Heart weight was 120 grams (A 3199). Dilatation was most marked in the right chambers.

Light of the same 29 human cases had aneurysmal formation as follows: at the level of the left ventricular apex in 6 and in the posterolateral portion of the left ventricle in the subvalvular zone of the mitral valve in 2.

Fig. 2 (A 3199) shows an aneurysmal dilatation in the superior portion of the posterior wall of the left ventricle. When seen from the inside of the left ventricle this area shows translucency of the wall behind and below the posterior leaflet of the mitral valve.

Fig. 3 (A 3286) is from another case with striking thinning of the left ventricular wall at two places. One site is at the apex and the other is in the posterior wall at the level of the atrioventricular sulcus immediately behind the posterior mitral leaflet. This zone also shows aneurysmal formation 3.5 cm in diameter which extends through the thinnest artery. It is important to emphasize that not all the attenuated areas showed aneurysmal dilatations.

Thinning and fibrosis were equally evident in the experimental animals. Fig. 4 is from a dog (15118) with a 21-month-old infection. Fibrotic foci (localized at the subpericardium) are observed at the apices of both the left and the right ventricles more extensively at the inferior portion of



Fig. 3 Anteroposterior section parallel to the interventricular septum (A3786). Marked dilatation of the LV chamber and an increase in trabeculation observed. Heart weight was 785 gram. Significant dilatation of the free ventricular wall seen at the apex and in the superior aspect of posterior wall of the LV. The latter one localized below the AV ring and behind the posterior mitral leaflet shows a 3.5-cm aneurysm. Histologically the consisted of dense collagenous connective tissue with a lot of muscular fibers undergoing variable degrees of degeneration (Gomori trichrome $\times 320$).

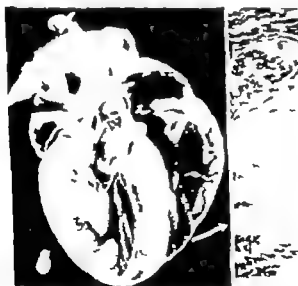


Fig. 4 Dog heart (LXI 198) as seen from its posterior aspect. Duration of 5 c. infection 2 months. Marked dilatation of the RV chamber and in lower degree of the RA are seen. Thickening of the wall at the inferior aspect of the anterolateral surface of the RV. Intramural thrombus adhered to the endocardium. Extensive fibrosis consisting of collagenous connective tissue and muscular alet. Fibrotic plaques became confluent near the subpulmonary (Gomori trichrome $\times 150$).

the anterolateral surface of the right ventricle. The ventricular wall is considerably diminished at this level having a thickness of 0.5 mm at the most affected portion.

In both the human and animal hearts an attempt was made by the use of serial sections to find vascular changes especially around the compromised tissues. Arterial or arteriolar lesions were not found in any of the cases studied. No necrotic areas were found in either the sites of wall thinning or in any other myocardial region.

II. Microscopic anatomy. Fibrotic foci were found in the markedly thin regions of the free ventricular walls. Histologically these were composed of collagen fibers. In those cases depicted in Figs. 1 and 2 the translucent zones were 1 mm in thickness and were composed of scar connective tissue and scanty inflammatory infiltrates.

Similarly the marked thinnings observed in the hearts of chronically infected dogs were composed predominantly of collagen fibers and some mononuclear cell infiltrates. In some dogs the Leishmanial form of the parasites were present in the myocardial fibers. The parasites were not encountered in human hearts.

Fig. 4 (LXI P8) shows in the anterolateral surface of the right ventricle a 0.5 mm thin area which is formed by dense collagenous connective tissue with some islets of muscular fibers that show various degrees of degeneration and few inflammatory infiltrates.

Muscular fibers located within fibrotic tissue were more abundant in the less involved areas. These islets of muscle with variable degenerative changes are particularly evident in the subepicardium on the

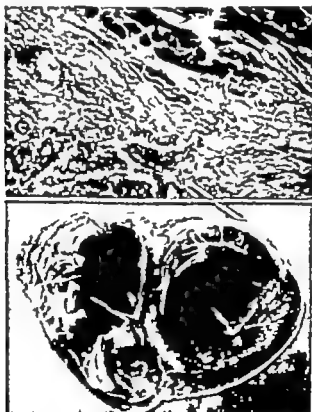


Fig. 5. Transverse section of the superior third of a human heart (V 3183). Marked dilatation of both ventricular chambers and the right ventricular outflow tract observed. Fibrous ring of the LV posterior wall consisting of a fibrous plaque which is most dense at the subendocardium. The plaque consists of collagenous connective tissue and muscular islets. The latter are scarce in the subendocardium but become numerous as the subepicardium is reached where lamellae are more dense and well preserved (Gomori trichrome $\times 250$).

other hand fibrous tissue predominates in the subendocardium. The mononuclear cell infiltrate was greater in those subepicardial areas in which muscular islets were more numerous.

Fig 5 (A 3183) shows a heart with dilatation of both ventricular chambers. The posterior wall of the left ventricle is moderately thinner than the posterior wall of the right ventricle. It consists of a plaque of dense subendocardial fibrous tissue. Histologic study showed fibrous tissue with few inflammatory infiltrates in the subendocardium and collagenous plaques with interposed muscular islets in the subepicardium. Variable degenerative changes were observed in the muscular fibers.

The microscopic study of the coronary system indicated an absence of atherosclerotic degenerative lesions in both the arterial and arteriolar segments. This was also true in the vessels located around the thin fibrotic areas.

III Correlation between histologic and

electrocardiographic findings A study of the morphology of ventricular complexes of supraventricular or ectopic origin demonstrated the presence of areas of fibrosis.

Fig 6 is from a patient (A 1731) with chronic Chagas myocarditis. The heart weighed 600 grams and showed marked dilatation of all chambers. The thickness of both ventricular walls was markedly diminished. Extensive confluent scars which formed large fibrous plaques were observed at the anterior surface of the left ventricle from the antero-septal region to the apex. An aneurysm 1.5 cm in diameter was observed at this level. Equally large fibrous plaques were observed on the anterior surface of the right ventricle becoming more confluent in the trans-trabecular area. The electrocardiogram showed first-degree AV block, notched full P wave of 0.12 sec duration in the standard leads and biphasic with slow negative phase in Precordial Lead V₁, slightly acuminate in Leads II and V₇. QRS and P voltages were similar.

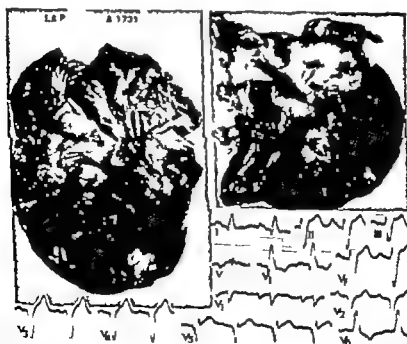


Fig 6 Correlation between histologic and electrocardiographic findings in case A 1731. Ventriculogram shows morphologies of type CS and V₁ and QRS in V₁-V₆ indicating presence of nonexcitable tissue oriented toward the anterior surface of the heart. Marked dilatation of the heart. Heart weight was 600 grams. Extensive fibrous plaques on the anterior surface of the heart (trabecular zone of RV, antero-septal surface and apex of LV). V₁ oriented toward the apex shows a discrete positive deflection of the ST-T segment indicating the presence of an aneurysm at the V₁ apex. The coronary system was intact.

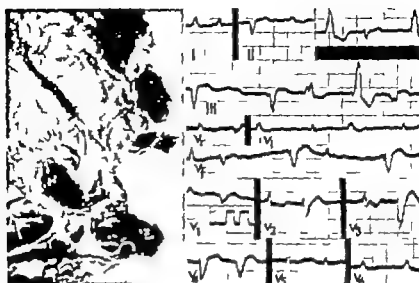


Fig. 7 Gross correlation and ECG (case V 2199). Extrasystolic complexes of QS type in V_4 and V_5 and qrs morphology in V_2 and V_3 indicate the presence of a posteroinferior nonexcitable zone. Extrasystolic QS from V_1 to V_4 and the decrease in R in the extrasystolic complex in V_5 indicate an anteroseptal and LV posterior wall zone. There was thinning and confluent fibrosis in these areas with large irregular plaques in the posteroinferior and anteroseptal apex and apex of the LV. The posteriority of the ST T in V_1 to V_4 correspond to myocardial infarction in the pex. The coronary system was intact.

in the left ventricle. These changes correlate well with the marked dilatation observed in both atrial chambers. QS complexes observed in Leads V_2 to V_3 indicate the presence of an electrically inactive zone throughout the anterior surface of the heart. Histologic sections of the anterior surface of both ventricles demonstrated that the fibrous plaques present consisted of dense collagenous connective tissue with small muscular bundles and few inflammatory infiltrates. The wall was composed exclusively of collagenous connective tissue at the level of the isthmus and apex of the left ventricle.

The heart depicted in Fig. 7 (V 2199) showed marked dilatation and a decrease in ventricular wall thickness. The wall was 10 mm thick in the superior portions but decreased to 2 mm at the apex. There was a diffuse fibrosis throughout the wall and this became interrupted at the apex and at the antero-septal and posteroinferior surfaces of the left ventricle forming quite extensive irregular plaques. Several aneurysms with thrombi were observed at the left ventricular apex. The electrocardiogram showed a complete arrhythmia due to atrial fibrillation and frequent multifocal

ectopic beats. The extrasystolic morphology is of the QS type in Leads II and III and of the qrs type in Lead V_2 indicating the presence of an unexcitable area at the posteroinferior surface of the heart. Extrasystoles of the QS type are observed in Pre-cordial Leads V_1 and V_4 . A significant decrease in the R voltage in the extrasystolic complex is observed from Lead V_4 to Lead V_5 ; these changes suggests a nonexcitable zone at the antero-septal and apical surfaces of the left ventricle. The ventricular wall was found to be formed by dense collagenous connective tissue and a few bundles of muscle fibers forming isolated islets.

The electrocardiographic tracings in animals demonstrated a correlation with those recorded in human beings. Fig. 8 shows the heart of an animal with a chronic infection; there is a marked dilatation and decreased thickness of the free ventricular walls. Fibrous and irregularly distributed plaques are observed on the epicardial surface and at the lateral surface of the right ventricle. The wall is formed by collagenous connective tissue and a few inflammatory infiltrates in the inferior and trabecular regions. Confluent interstitial connective tissue and intermediate muscular islets are seen in the

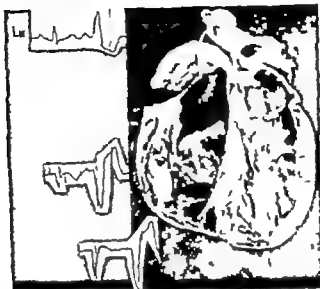


Fig. 8. A similar correlation in a dog with chronic *S. cruzi* infection of 3 years duration. Unipolar epicardial tracings of supraventricular and ectopic ventricular origins (RV) obtained at the trabecular zone show morphologies of the QS type indicating the presence of a nonexcitable zone in the area neighboring the one studied. Those of the lateral aspect of the RV wall show morphologies of QRs type in the supra-ventricular complexes and of QS type in those of ectopic origins. The trabecular zone consisted of collagenous connective tissue. The lateral aspect showed interstitial connective tissue confluent in the subendocardium and subepicardium forming dense areas of fibrosis. The medial portion of the wall showed muscular islets surrounded by collagenous connective tissue. The coronary system was normal.

subendocardium and subepicardium at the middle zone. Unipolar epicardial tracings from the inferior and trabecular zones showed QS morphology in supraventricular or ectopic complexes originating in the right ventricular wall. Supraventricular complexes obtained at the middle zone of the right ventricular wall showed QS morphology. Extrasystolic complexes originating in the right ventricle were of the QS type. These findings suggest the presence of a nonexcitable zone adjacent to the origin of the leads which coincides with the areas of fibrosis described.

Discussion

Flaccidity and dilatation are commonly seen in chronic inflammatory cardiopathies both in those of *S. cruzi* origin^{1, 9, 11, 22} and in those of any other etiology.^{20, 21, 23} Flaccidity was found in all of our human and experimental cases. Dilatation of the chambers was marked in 25 of the autopsies cases moderate in 1 (A 2503) and slight in 3 (A 2769, A 3057 and A 3293). The left atrium was less affected by dilatation in those cases of slight or moderate hypertrophy, but showed

a dilatation proportional to that of the other chambers when hypertrophy became marked. In 2 of the cases with slight cardiac enlargement (A 3057 and A 3293) the right chambers were affected the most. In the third case (A 2769) dilatation was evident in both ventricles. The cases with marked enlargement showed dilatation of all chambers with no particular pattern of predominance.

Intramural thrombosis was a frequent finding as demonstrated by Tejeda and Castro⁹ and Franco de Oliveira.⁷ The frequency of this finding was 79.3 per cent in our study in the human cases with predominance of the right chamber (right atrial appendage-RAAp 3.4 per cent, RA 38.9 per cent, RV 24.1 per cent) as compared to the left chambers (LA 3.4 per cent, LV 51.7 per cent). No thrombi were found in the left atrial appendage (LAAp) or in the right ventricular outflow tract (RVOT) in spite of the marked degree of dilatation evident in both the LAAp and the RVOT. Independently of other chambers, the left ventricle showed a higher frequency of thrombi than did the right ven-

tricle as has been reported previously by Tejada and Castro.⁸

In general hearts with more marked dilatation showed a greater frequency of thrombosis in the various chambers although marked cardiomegalies without accompanying thrombosis were also observed (A 3116 A 3183 and A 3247). In general slight dilatations are not accompanied by thrombosis in our 3 cases thrombi were not found in 2 (A 2769 and A 3057) and a left ventricular thrombosis was seen in 1 (A 3293). It was noted that the thrombosis appeared in a left nondilated chamber.

Laraja and associates²⁷ found that chronically infected dogs showed after a few months hypertrophy of the right chambers. In our series dilatation was found in all chambers in advanced stages of the disease predominance of the right chamber was observed only in the early phases. In mural thrombi were found in 11 per cent of the animals with chronic infection as compared with a higher percentage in human beings these thrombi were localized 8 per cent in the right ventricle and 3 per cent in the left ventricle.

Thinning of the free ventricular walls was a frequent finding in our autopsy material. Similar findings had been reported earlier in pathologic studies of chronic Chagas myocarditis.^{19,20} Diaz and associates¹ and Laraja and associates²⁷ stressed the frequency of thinning, at the left ventricular apex is produced by confluent fibrosis²⁸ which subsequently produces aneurysmal dilatation at times.^{23,24} Mori² reported the first case with thinning and aneurysmal formation in a different localization. Two of his 3 cases presented the classic findings but the third one had aneurysmal formation in the anterior surface of the left ventricle below the aortic ventricular sulcus. Frequency and distribution of thinning and aneurysmal formation were analyzed from a statistical point of view by Suarez²⁹ whose figures are very similar to those in the present study.

Chagas infection causes in animals (monkeys dogs etc) a degeneration of cardiac fibers and the proliferation of fibroblasts in a relatively short period of time. These changes appeared in some of our animals during the fourth week after primary infection coincidental with an intense inflammatory infiltrate. Torres and

Tayres³⁰ found that degeneration of cardiac fibers becomes evident 3 months after inoculation in the species *Macacus cebus*. This period can be considered to be a time of expected fluctuation in the appearance of fibrotic lesions in experimental myocarditis. Fibrosis appeared very early in some of our dogs with a decrease in the thickness of the wall being evident 21 months after the primary infection. Thinning plus extensive fibrosis were more common in the free wall of the right ventricle in experimental animals.

Microscopic study of the thin areas demonstrated that the histologic pattern is the same in human and experimental cases. When thinning is extreme (foliaceous type) and extensive fibrous plaque is found which consists of collagenous fibers and almost no inflammatory infiltrate. In less extensive lesions bundles of muscular tissue are seen within the fibrous tissue these islets show fibers undergoing variable degenerative processes and are more numerous in the cases of less pronounced thinning. Mononuclear cell infiltrate is greater in those areas in which islets are abundant.

Laraja and associates explain the decrease in the thickness of the wall as a result of extensive destruction of myocardial fibers together with replacement by connective tissue. The destruction is the result of a diminishing supply of blood which is in turn secondary to hyperplasia of the intima and thickening of the medial articular layer with a subsequent reduction in the caliber of the lumen of the vessel. Weinrich and associates⁴ interpret the fibrosis as scarred infarcts which result from the inflammation of capillaries arterioles and perivascular tissue which produces coronary thrombosis. Coronary or necrotic lesions were not found in our study therefore the fibrosis cannot be ascribed to myocardial infarction.

Mori² did not find arterial lesions in 2 of his 3 patients but reported moderate arteriosclerotic lesions in the larger coronary branches in the third one a 52 year old woman. Tejada and Castro⁸ failed to find vascular changes in 8 patients with widespread fibrosis. On the basis of all these reports it is our thought that fiber degeneration and fibrous replacement with subsequent thinning of the wall cannot be

explained by ischemia due to coronary occlusion.

Most believe that the causative factor is the myocardial inflammatory process originated by the disease per se. He suggests that the dense fibrosis of limited areas is related to regions in which inflammation and destruction of muscular elements are more intense. Pifano and associates¹⁰ and Anselmi and associates¹¹ demonstrated that the close relationship between the degree of degeneration of muscular elements and the intensity of the inflammatory process in experimental myocarditis originated from alterations in the supply of oxygen caused by increases in the interstitial space due to edema and inflammatory infiltrate. In chronic Chagas myocardiopathy it has been possible to demonstrate that rapid ventricular complexes in the electrocardiogram identify electrically nonexcitable zones which correspond to fibrous areas¹²⁻¹⁴; this has been confirmed in our study in both autopsy and experimental series. Nonexcitable zones are related to a predominance of fibrous tissue in the areas to which the exploratory electrode is directed. Replacement of muscular tissue by collagen fibers caused important changes in supra-ventricular and ectopic ventricular ventriculograms. QR, Qr and QS extrasystolic morphologies indicative of nonexcitable zones were the ones most usually observed. An analysis of the different leads permitted an appraisal of the localization and extent of the areas of fibrosis. The physiopathology of ventricular activation which originates these morphologies has been demonstrated in experimental studies¹⁵⁻¹⁷; their appearance depends on the presence of ventricular fibrosis or necrosis.

In cases of aneurysmal dilatation it was possible to observe the characteristic imbalance of the ST-T segment which is pathognomonic of these pathologic findings¹⁸. Even when electrocardiographic findings of ischemia are related to the presence of inflammatory infiltrates in Chagas myocardiopathy¹⁹ the combined presence of nonexcitable tissue and areas of injury should suggest the presence of aneurysms in the wall.

Summary

Histologic findings in 29 individuals with a clinical picture of chronic Chagas

myocardiopathy are analyzed. Both macroscopic and microscopic changes are studied and are correlated with similar findings in dogs infected with strains of *Schizotrypanum cruzi*.

Flaccidity and dilatation was frequently found in both the human and experimental cases. Dilatation was more common in the right chambers of the hearts of the dog, particularly in the right ventricle. Intramural thrombosis was frequent in human subjects (79.3 per cent) but was observed with less frequency in animals (11 per cent). Thinning of the wall and plaques of fibrosis were found respectively in 72.4 and 42 per cent of the cases in the human and animal groups. Parietal aneurysms localized in the areas of fibrosis and thinning were found in 27.6 per cent of the autopsy cases. Aneurysms of the wall were not found in dogs but they were seen in the trabecular zone of the right ventricle in 7 animals. Aneurysms were of variable diameter (1 to 3 cm) and disappeared when the animal died. Thinning of the wall by fibrous replacement of muscular tissue was found in all of the cases.

The histologic pattern of the thin areas was similar in both groups: large areas of collagenous connective tissue at the sub-endocardial level were found. Also islets of muscular bundles were found at mid wall and subepicardium. They were particularly abundant in the latter localization.

An electrocardiographic correlation demonstrated that epicardial unipolar leads obtained at the areas of fibrosis in dogs had the ventricular morphology of nonexcitable zones. In human beings ventriculograms of both supraventricular and ectopic ventricular origin always indicated the presence of areas of fibrosis; the localization and extent of which could always be determined by an analysis of the different leads.

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Reduction in cardiovascular and metabolic responses to phenylephrine in acutely pancreatectomized dogs

Leifur Goldberg, M.D.*

Ira Rosenblum, M.D.**

(Albany, N.Y.)

To date a number of diverse factors which can alter the cardiovascular responses to sympathomimetic amines have been reported. Among these are the functions of the endocrine organs, the thyroid gland being one which has recently received much experimental attention.¹ Less attention has been directed to the pancreas despite the known interrelationship between its insulin secretory activity and the secretion of catecholamines by the adrenal medulla.²

Some reports in the clinical literature indicate an increased tendency toward hypertension in diabetics, although this may be traceable to such changes as capillary glomerulosclerosis and arteriosclerosis rather than to any altered responsiveness to endogenous catecholamines. Experimentally however in alloxan diabetic rats a heightened vascular reactivity to both epinephrine and norepinephrine has been noted.³

The purpose of the present experiments has been to investigate a possible relationship between pancreatectomy and the cardiovascular responses to sympatho-

minetic amines. The acutely pancreatectomized dog was chosen for these studies rather than the alloxan treated animal because of the well known ability of alloxan⁴ to produce renal lesions which may complicate the interpretation of experimental results. Furthermore, acute pancreatectomy rather than chronic pancreatectomy is less likely to cause the development of metabolic disorders, among them acidosis,⁵ which itself can alter the cardiovascular responses to sympathomimetic amines.

Methods

Thirty nine dogs of both sexes, weighing between 20 and 35 kilograms were used. These were fasted 16 to 24 hours before the experiment and then were anesthetized with an intraperitoneal injection of 0.67 ml per kilogram of a solution containing pentobarbital sodium (60 mg. per milliliter), ethyl alcohol (10 per cent volume per volume), propylene glycol (20 per cent volume per volume) and water (Dibutal®).

Tracheotomy was performed and a

From the Department of Pharmacology, Albany Medical College, Albany, N.Y.

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metal T tube was inserted into the trachea. Polyethylene cannulas were placed in the femoral vein for the administration of drugs and in the common carotid artery. The latter cannula was attached to a Statham P23Db blood pressure transducer for the recording of arterial blood pressure. This cannula was also used to obtain samples of arterial blood. After a median sternotomy artificial respiration was begun with compressed air with the use of a respirator valve. The respirator valve was adjusted by visual observation of the degree of inflation of the lungs.

The pericardium was opened through a lengthwise slit and a Walton Brodie strain gauge arch was sutured to the surface of the ventricle. The ventricular rate was recorded by applying the electrical output of the strain gauge arch to a heart rate meter. Arterial blood pressure, myocardial contractile force and heart rate were recorded simultaneously with an ink writing oscillograph.

Procedure for pancreatectomy. The abdomen was entered through a midline incision extending from the xiphoid process to a few centimeters distal to the umbilicus. Clamps were placed around the small intestine at the gastroduodenal junction and about 15 cm distally. The dorsal pancreatic duct, ventral pancreatic duct, cranial and caudal pancreaticoduodenal arteries and veins, pancreatic branches of the splenic and hepatic arteries and veins and the mesenteric blood vessels were all clamped. The right and left lobes of the pancreas together with the clamped section of the bowel were then excised *en masse*. Hemorrhage was controlled with electrocautery and by clamping.

Sham-operated animals were prepared in much the same way. The bowel was clamped at the identical sites and the small mesenteric blood vessels were clamped. In addition, other clamps were placed in the abdomen but these did not occlude the pancreatic ducts or any of the pancreatic blood vessels. The pancreas and bowel were then left in situ. The incisions in the skin were closed with sutures after both surgical procedures had been completed. In both pancreatectomized and sham-operated animals a period of approximately 90 minutes was allowed to lapse before infusion of a drug was begun.

Samples of arterial blood were drawn into heparinized test tubes at the end of the 90-minute postoperative period and again during the peak of the cardiovascular responses to infusion of a drug. These samples were analyzed for plasma glucose by the Glucostat method for serum potassium by means of a Technicon Auto-analyzer and for pH with the use of a blood pH electrode and an Instrumentation Laboratories pH gas analyzer. This latter analysis was performed at 37°C.

The following drugs were used: crystalline zinc insulin (insulin L 40*) *dl*-isoproterenol HCl and *l*-phenylephrine HCl. The doses of the latter two drugs are expressed as amounts of their free base.

The Student *t* test¹⁰ was used to determine the significance of a difference between groups of animals and the term significant difference is used to denote a *P* value of 0.05 or less unless otherwise stated.

Results

Effects of infusion of phenylephrine in normal dogs. Three doses of phenylephrine 1.0, 3.0 and 10.0 µg per kilogram per minute were infused for approximately 15 minutes in a total of 12 dogs. 4 dogs were used at each dose level. The cardiovascular changes observed were an increase in systolic pressure and contractile force, accompanied by a reduction in heart rate. Hyperglycemia was also produced particularly by the highest dose of phenylephrine but no hyperkalemia such as has been reported for other pressor amines¹⁰ was observed. These observations are summarized in Table I. Arterial pH was also measured and the mean value for all 12 dogs during infusion of phenylephrine was 7.48 ± 0.15 E, which was not significantly different from the mean pre-infusion control value of 7.50 ± 0.15 E.

Effect of acute pancreatectomy on the responses to phenylephrine. Acute pancreatectomy was performed in 12 animals. The pancreatectomy resulted in a preparation which did not differ significantly in any of the preinfusion control cardiovascular or metabolic parameters from those measured in normal dogs. Thus the mean plasma glucose value for all normal dogs was 147 ± 11 SE mg. per cent and that for

Table 1 Cardiovascular and metabolic responses to 1 phenylephrine in 12 normal and 12 pan-creatoctomized dogs^a

Phenylephrine ($\mu\text{g}/\text{kg}/\text{min}$)	Systolic pressure (mm Hg)	Contractile force (Δ)	Heart rate (beats/ min)	Glucose ($\text{mg}/100 \text{ c.c.}$)	Potassium (mEq/L)
Normal					
Control	114 ± 10		207 ± 05	134 ± 04	3.9 ± 0.1
10	136 ± 12		203 ± 07	132 ± 10	4.0 ± 0.2
Mean change	$+22 \pm 03$	0	-4 ± 07	2 ± 07	$+0.1 \pm 0.1$
Normal					
Control	113 ± 18		204 ± 07	150 ± 12	4.5 ± 0.2
30	177 ± 17		188 ± 09	172 ± 17	4.5 ± 0.3
Mean change	$+64 \pm 07$	$+34 \pm 08$	-16 ± 07	$+22 \pm 09$	0
Normal					
Control	101 ± 10		204 ± 05	158 ± 04	4.1 ± 0.1
100	245 ± 11		178 ± 07	240 ± 19	4.3 ± 0.2
Mean change	$+144 \pm 07$	$+117 \pm 10$	-26 ± 07	$+82 \pm 18$	$+0.2 \pm 0.2$
Ia castration					
Control	109 ± 18		211 ± 11	128 ± 13	4.0 ± 0.2
30	134 ± 18		201 ± 12	143 ± 12	3.8 ± 0.3
Mean change	$+25 \pm 03$	0	-10 ± 04	$+15 \pm 10$	-0.2 ± 0.1
Pin castration					
Control	97 ± 06		207 ± 06	155 ± 20	3.8 ± 0.1
70	154 ± 06		172 ± 04	198 ± 29	4.0 ± 0.2
Mean change	$+57 \pm 09$	$+52 \pm 11$	-30 ± 05	$+43 \pm 11$	$+0.2 \pm 0.1$
Ia castration					
Control	95 ± 08		221 ± 07	216 ± 14	4.1 ± 0.1
100	179 ± 11		203 ± 02	249 ± 16	4.1 ± 0.1
Mean change	$+84 \pm 06$	$+66 \pm 08$	-18 ± 04	$+33 \pm 06$	0

For each of the 11 genotypes and 4 values obtained, regression curves \pm S.E. + d.m. points and 11 sag

all pancreatectomized dogs was 162 ± 14 S.E. mg per cent. Other control values were systolic pressure 97 ± 25 mm Hg, for pancreatectomized dogs and 110 ± 2 S.E. mm Hg for normal dogs; heart rate 211 ± 14 S.E. beats per minute for pancreatectomized dogs and 205 ± 3 S.E. beats per minute for normal dogs. The mean arterial blood pH was 7.45 ± 0.1 S.E. in the pancreatectomized dogs.

These pancreatectomized dogs were infused with one of three doses of phenylephrine either 30, 70 or 100 $\mu\text{g}/\text{kg}$ per minute 90 minutes after pancreatectomy. A markedly smaller rise in mean systolic pressure was observed in these dogs and this difference is evident in a comparison of the dose response curves of the two types of dogs (Fig. 1). Further statistical comparisons between these groups of dogs were made at the two complementary doses of

30 and 100 $\mu\text{g}/\text{kg}$ per minute. These comparisons (Table I) show the occurrence in pancreatectomized dogs of a significant change in response to the effects of phenylephrine on mean systolic pressure, heart rate, contractile force and plasma glucose at a dose of 10 $\mu\text{g}/\text{kg}$ per minute and on mean systolic pressure and contractile force at a dose of 30 $\mu\text{g}/\text{kg}$ per minute. It is evident therefore that acute pancreatectomy can reduce the cardiovascular and metabolic responses to infusions of phenylephrine.

Partial restoration of the pressor response to phenylephrine with insulin When the effect of an infusion of 100 μ g/kg per minute of phenylephrine on systolic pressure is calculated from observations in pan-crectomized dogs is 2 per cent of the response in normal dogs a value of 58 ± 5 SE per cent is obtained (Fig. 2). Expen-

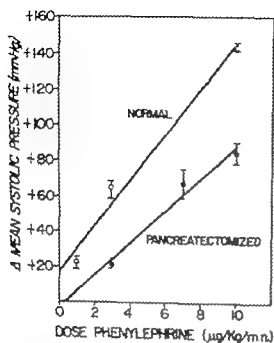


Fig. 1 The dose response curves to the pressor response to infusions of graded doses of phenylephrine in 12 normal and 12 pancreatectomized dogs. Each point represents the mean \pm SE response observed in 4 dogs. Each dog was used once for a single infusion of phenylephrine.

ments were performed in 9 pancreatectomized dogs with phenylephrine (10.0 μ g/kg per minute) to which various amounts of crystalline insulin were added in order to determine whether this pressor response could be restored to that seen in normal dogs. Three doses of insulin, either 1, 2 or 3 units per kilogram were mixed with the dose of phenylephrine and both were infused together. The results (Fig. 2) show that a dose of 2 units of insulin per kilogram caused a partial restoration of the pressor response to 82 ± 4 SE per cent of normal and this pressor response was significantly greater than that produced in pancreatectomized dogs by 10.0 μ g/kg per minute of phenylephrine without the addition of insulin. The addition of 1 or 3 units of insulin per kilogram did not however cause a significant restoration of the pressor response to phenylephrine. The addition of 2 units of insulin per kilogram although partially restoring the pressor response to phenylephrine produced no significant restoration of the chronotropic or inotropic responses; these were a decrease in rate of

30 ± 7 SE beats per minute and an increase in force of contraction of 84 ± 27 SE per cent not significantly different from the decrease in rate of 18 ± 4 SE beats per minute and the increase in contractile force of 66 ± 8 SE per cent observed without the addition of insulin to the infusion (Table 1). No consistent changes in plasma glucose occurred from infusion of phenylephrine and insulin; in 2 dogs it fell 10 mg per cent and in the third a rise of 79 mg per cent occurred with the addition of 2 units of insulin per kilogram. A similar inconsistency was also evident in the pancreatectomized dogs receiving phenylephrine and 1 or 3 units of insulin per kilogram. Therefore the expected hyperglycemic effect of phenylephrine must have been opposed by a hypoglycemic effect of insulin in some experiments.

Effects of isoproterenol in normal and

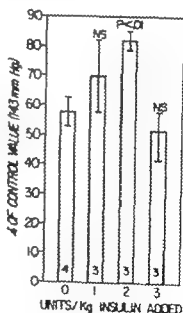


Fig. 2 The partial restoration of the pressor response in pancreatectomized dogs to phenylephrine 10 μ g per kilogram per minute by the addition of various doses of crystalline insulin. The results are expressed as the mean \pm SE per cent of the response to infusion of 10.0 μ g per kilogram per minute of phenylephrine in a normal dog. Where response was significantly different from that observed to phenylephrine without insulin the P value is given. NS and $P<0.01$ indicate that no significant difference was observed. The numbers in the lower portions of the bars indicate the number of dogs used.

Table II Cardiovascular and metabolic responses to *dl* isoproterenol in 3 normal and 3 pancreatectomized dogs*

Isoproterenol ($\mu\text{g/kg/min}$)	Diastolic pressure (mm Hg)	Contractile force (Δ)	Heart rate (beats/min)	Glucose (mg/100 cc)	Insulin (mEq/l)
Normal					
Control	92 \pm 12		225 \pm 08	126 \pm 06	4.5 \pm 0.1
1.5	33 \pm 06		249 \pm 02	259 \pm 09	1.7 \pm 0.1
Mean change	59 \pm 06	+112 \pm 21	+23 \pm 05	+98 \pm 19	-0.8 \pm 0.3
Pancreatectomy					
Control	95 \pm 15		197 \pm 12	126 \pm 06	4.0 \pm 0.1
1.5	33 \pm 11		239 \pm 10	224 \pm 17	3.0 \pm 0.1
Mean change	-63 \pm 04	+121 \pm 10	+41 \pm 03†	+90 \pm 17	-1.0 \pm 0.1

Values represent mean \pm S.E. * $p < 0.05$ vs. control. † $p < 0.05$ vs. normal dogs. ‡ $p < 0.05$ vs. control.

pancreatectomized dogs. The effects of pancreatectomy on the responses to a vaso-depressor amine isoproterenol were studied in 3 normal and 3 pancreatectomized dogs. An infusion of 1.5 $\mu\text{g/kg}$ per minute of isoproterenol in normal dogs caused an average fall in mean diastolic pressure of 59 ± 6 S.E. mm Hg (Table II). This response was also accompanied by an increase in myocardial contractile force, an increase in heart rate and both hyperglycemia and hyperkalemia (Table II). The same dose of isoproterenol when infused into pancreatectomized dogs caused changes in diastolic pressure, contractile force, plasma glucose, and plasma potassium which were not significantly different from those observed in normal dogs, only the increase in heart rate was significantly different from the response in normal dogs.

Discussion

The interrelationship between insulin and the secretion of catecholamines has now been demonstrated in a number of ways. One such example is the classic demonstration by Cannon and associates¹¹ who showed that insulin induced hypoglycemia results in an increased secretion of catecholamines and a subsequent amine induced mobilization of glucose. The principal source of the catecholamines which consist mainly of epinephrine would appear to be the adrenal medulla.¹² This insulin evoked secretion of epinephrine can evoke a cardiovascular as well as a meta-

bolic response. The cardiovascular response has been reported to consist of a fall in diastolic blood pressure and tachycardia.¹² Presumably too a reduction in the secretion of insulin should be followed by a reduction in the secretion of catecholamines by the adrenal medulla. Thus a feedback mechanism wherein insulin can affect catecholamine supported hemostasis exists in theory.

The present experiments have demonstrated that acute pancreatectomy in dogs reduces the cardiovascular and metabolic responses to one pressor amine and thereby extends the connection between insulin and sympathomimetic amines to a drug which does not exist endogenously. It is also evident that this interrelationship does not extend to all sympathomimetic amines since the responses to isoproterenol were largely unaffected by pancreatectomy.

That these observations with phenylephrine in pancreatectomized dogs involve a deficiency of insulin at least in part is evident from the partial restoration of the pressor response to phenylephrine by the addition of an appropriate amount of insulin. It is also evident that other factors among them acidosis could not have been responsible for the reduced response to phenylephrine since our observations clearly show that no significant change in arterial blood pH resulted from acute pancreatectomy. Changes in plasma sugar can also be excluded since no significant change in plasma glucose occurred in the 90 min

utes after pancreatectomy. Nonetheless there is reason to suppose that subtle changes due to lack of insulin were occurring during this time for Wrenshall and associates¹² have shown that a reduction in the utilization of glucose by skeletal muscle takes place within one-half hour after pancreatectomy in dogs and others¹³ have shown that the utilization of glucose in rats is decreased within 2 hours after acute pancreatectomy. One may speculate then that some manifestation of a deficiency of insulin was present in our pancreatectomized dogs.

An important locus at which a deficiency of insulin could be manifested is the cell membrane where insulin acts to facilitate the transmembrane transport of sugars¹⁴ and amino acids¹⁵ including phenylalanine. Since phenylephrine resembles the amino acid phenylalanine in structure one could speculate that the reduced responsiveness to phenylephrine resulted from a reduced intracellular penetration in the absence of insulin. Evidence now exists that the cardiovascular effects of α -phenylephrine are in part derived from the release of endogenous catecholamines¹⁶ which are stored intracellularly.¹⁷ The failure of phenylephrine to gain access to these stores would leave only direct adrenergic receptor activation as a mechanism for its diminished cardiovascular and metabolic effects.

Summary

The cardiovascular and metabolic responses to α -phenylephrine were studied comparatively in groups of normal and acutely pancreatectomized dogs. Pancreatectomy in dogs had the effect of reducing the rise in systolic pressure, myocardial contractile force and plasma glucose as well as causing the reduction in heart rate which was produced by an infusion of phenylephrine 10.0 μ g per kilogram per minute. The responses to infusion of isoproterenol however were not generally altered by pancreatectomy. Of the changes in response to phenylephrine due to pancreatectomy, the addition of 2 units of insulin per kilogram to the infusion was able to restore partially the pressor response. It may be speculated that these results indicate a role for insulin in facilitating the response to sympathomimetic amines which act to

some extent on intracellular stores of endogenous catecholamines.

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Diastolic murmur of equine aortic insufficiency

David L. Smiley D I M M Sc*

Sanford Bishop D I M W Sc **

C Roger Smith D I M Ph D ***

Columbus Ohio

The literature contains little information concerning either the diastolic murmur or the valvular lesions of aortic insufficiency in horses. That which is available consists primarily of phonocardiograms of the murmurs with little definitive information in regard to valvular lesions.¹⁻⁴ Availability of a large population of aged horses and mules at an abattoir has afforded the authors an opportunity for antemortem and postmortem studies of aortic insufficiency in these animals. The purpose of this report is to describe briefly the valvular lesions of aortic insufficiency in horses and mules and to describe the diastolic murmurs accompanying the lesions. A hypothesis of the origin of the presystolic accentuation present in some murmurs is presented.

Methods

Seventeen horses and 7 mules were selected for study on the basis of presence of a mammary Grade II (of VI) or greater which extended through most or all of diastole. All were over 10 years of age. General health ranged from apparently normal to poor. Others having a soft low

patched murmur restricted to early diastole were not included in the study.

Phonocardiograms (PCGs) were recorded from 19 unanesthetized animals. Murmurs in the other 5 were assessed by auscultation only. Sixteen PCGs were recorded with a Sanborn Twin Beam oscillograph at a paper speed of 75 mm per second. Logarithmic filtering was used. A Sanborn crystal microphone with a 15 cm bell was applied to the point of maximal intensity of the murmur. An electrocardiogram (ECG) usually Lead aV₁ served as the reference tracing.

Phonocardiograms were recorded from 3 horses with an eight channel Sanborn 50VI photographic oscillograph. The filter system was set at 100 cps cutoff. Phonocardiograms, ECC pneumogram and aortic pressure were recorded simultaneously at paper speeds of 50, 100 or 200 mm per second. Aortic pressure was recorded from 2 horses through polyethylene tubing (0.046 inch I.D.) with a Sanborn model 267B transducer. The left carotid artery was punctured percutaneously with a 14 gauge needle for introduction of a catheter. Aortic or left ventricular

pressures were recorded from one horse with a catheter tip transducer* frequency response flat to 100 cycles introduced via a surgically exposed carotid artery.

Phonocardiograms were analyzed for the following: intensity configuration as determined by variation in intensity and vibration frequency of the murmurs.

Hearts were collected immediately after slaughter and transported in an ice chest to the laboratory where they were examined for the presence of valvular and regurgitant or jet lesions. Fifteen hearts were examined grossly and microscopically. Six hearts were examined for gross lesions only. Postmortem examination of 3 hearts was not possible. The hearts of 12 horses and mules which did not have a diastolic murmur were examined for valvular lesions and served as controls.

Results

Gross pathology. A fibrous band located parallel to the free edge of at least one cusp of the aortic valve was the most consistent and significant valvular lesion found at postmortem examination (Fig. 1). A band extended across the entire cusp in some instances. In other instances it involved only a portion of a cusp. Usually the short bands extended from either commissure of the cusp; however in a few instances they were located at the center of the cusp. The free edge of those cusps with prominent band lesions appeared to be subject to eversion with insufficiency of the cusp occurring as a consequence. Observations supporting this impression will be discussed later. Of 21 hearts examined postmortem, 18 had significant band lesions on one or more cusps of the aortic valve. Bands were located on the aortic cusps of the 18 hearts and distributed in this manner: left coronary cusp in 12 hearts, right coronary cusp in 3 hearts, noncoronary cusp in 2 hearts, and both the left coronary and the noncoronary cusps in 1 heart. The free edge of each affected cusp was considered to be subject to eversion.

Nodules, variable in size, were found on

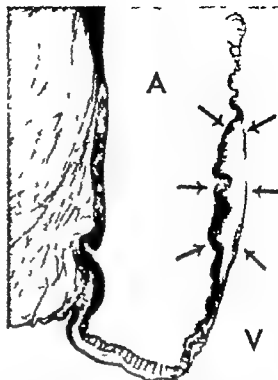


Fig. 1. Cross section of an aortic cusp illustrating a band lesion. The band is indicated by the arrows. The aortic surface is indicated by A and the ventricular surface by V. That portion of the cusp distal to the band probably everted after closure of the valve and thereby served as the vibrating structure in the generation of a mild aortic diastolic murmur. Orcein, an Gieson stain $\times 7$.

the ventricular surface or at the free edge of some aortic cusps.

No lesion considered as being compatible with the production of a diastolic murmur was found on the tricuspid, mitral or pulmonary valves.

Jet or regurgitant lesions consisting of irregular masses of connective tissue were present on the interventricular septum (Fig. 2), on base of the aortic cusps or on the ventricular surface of the anterior cusp of the mitral valve of 17 of the 21 hearts examined. Jet lesions were present on the interventricular septum ventral to the right coronary and noncoronary cusps in 12 of the hearts that had a major band lesion on the left coronary cusp of the aortic valve. Minor jet lesions were present on the bases of the right coronary and noncoronary cusps of some of the above mentioned 12 hearts. No jet lesion was



Fig. 1. Eruptant lesion located on the interventricular septum ventral to the aortic valve of a horse with insufficiency of the left coronary cusp of the aortic valve. The point of the arrow indicates prominent cusp-like ridges oriented toward the aortic valve. The seagull diastolic murmur recorded from this horse is illustrated in Fig. 3.

found in the thirteenth heart that had a band on the left coronary cusp. Jet lesions in the 3 hearts that had a band lesion on the right coronary cusp were located on the base of the left coronary cusp and on the ventricular surface of the anterior cusp of the mitral valve. In the 2 hearts that had band lesions on the noncoronary cusps, jet lesions were found below the right coronary cusp in one and below the left coronary cusp in the other.

Microscopic observations on valvular and jet lesions are described in another report.⁴

Diastolic murmurs. Diastolic murmurs were classified as either musical or noisy. Interpretation of musicality was based on the relative uniformity in the frequencies of the vibrations comprising the murmur (Fig. 3). Those murmurs considered to be noisy were composed of a mixture of vibrations of different frequencies (Fig. 4).

Musical diastolic murmurs. Thirteen animals had diastolic murmurs which were completely or predominantly musical. A

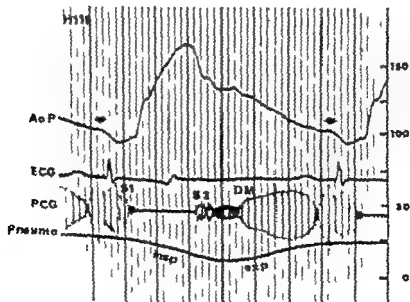


Fig. 3. Aortic pressure (AoP), electrocardiogram (ECG), phonocardiogram (PCG), and pneumograph (Pneumo) recorded simultaneously from a horse with insufficiency of the left coronary cusp of the aortic valve. The lead II ECG was used for the rhythm rather than recording aortic pressure. Arrows indicate that the aortic pressure was recorded in millimeters of mercury. The amplitude and frequency of the murmur are indicated by the scale bar. The time lines in this and in subsequent figures are at 0.04-second intervals.

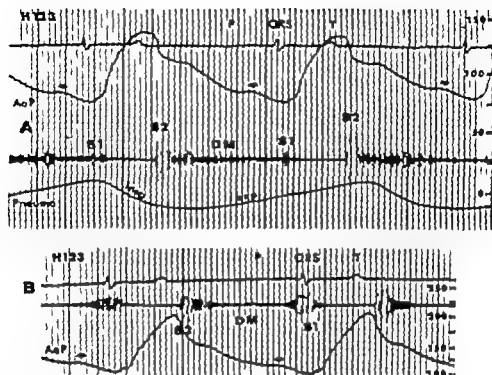


Fig. 4 ECG tracing, *aortic pressure* (AaP), *phonogram* and *pneumogram* (Pneum) recorded simultaneously from *birds with aortic insufficiency*. (A) Control (B) After intravenous administration of 2 mg of phenylphrine. *Aortic pressure* recorded through polythene tubing and expressed in millimeters of mercury. Red lines in (B) arrows indicate *intensity* of murmur. After the administration of phenylphrine (B) the *aortic pressure* increased and the murmur became more *intense* in *early diastole* and in *presystole* although it *remained* in *mid-diastole*.

postmortem examination was performed on the hearts of 10 of these. A prominent band lesion was found on at least one aortic cusp in all 10 hearts. By auscultation four murmurs were high pitched with a cooing quality (Figs 3 and 5A). These probably were comparable to the so called sea gull diastolic murmur in man.⁴ The remainder of the musical murmurs were low pitched with a rasping or buzzing quality (Figs 5B and 6).

The loudness of the musical murmurs ranged from Grade 2 to Grade 6 with the majority being either Grade 3 or Grade 4. The configuration as determined by a change in the intensity of the murmur during its course was variable from one animal to another. Minor variation was usually observed on a beat-to-beat basis. Peak intensity occurred at the termination of the second sound or shortly thereafter in some animals (Fig 5B) in mid diastole in others (Fig 5C) and in presystole in

others (Fig 5A). Three of the sea gull murmurs increased in intensity uniformly throughout their course. The intensity of another sea gull murmur increased abruptly after the P wave of the ICC (Fig 3). A prominent band lesion was present on the left coronary cusp of the aortic valve in those instances in which there was presystolic accentuation of the musical murmur.

In general the frequency of the vibrations of the musical murmurs was highest at the onset and decreased during the course of the murmur. The frequency of three sea gull murmurs decreased uniformly during their course. The frequency of another sea gull murmur decreased abruptly after the P wave (Fig 3). The presystolic murmur in one duck was higher pitched than the early diastolic murmur. In some instances it was difficult to establish the precise frequency of a murmur because of faster vibrations being superimposed upon

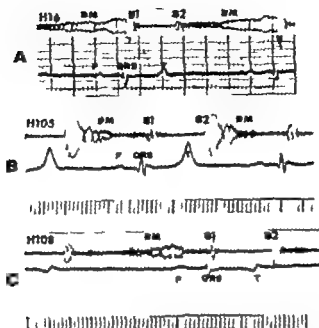


Fig. 5 Aural diastolic murmurs (DV) of aortic insufficiency recorded from 3 horses. Variability of the musical murmur of aortic insufficiency in the horse well exemplified. A Configuration of the murmur is generally crescendo with greatest amplitude occurring in presystole. B Greatest amplitude of the murmur occurs early in diastole followed by a secondary increase in amplitude. Murmur is noisy in presystole. C Musical element restricted to mid-diastole with abrupt termination after onset of P wave. Superimposition of vibrations of at least two different frequencies present in the musical element.

the slower vibrations of the fundamental frequency (Fig. 5 C).

Noisy diastolic murmurs. In general PCCs of the noisy murmurs were of little value for analysis; therefore auscultation was relied upon for assessing most of these. Many of the noisy murmurs were loudest at their onset or shortly thereafter and were generally decrescendo throughout. Peak intensity in others appeared to occur near mid-diastole. Ten of the eleven noisy murmurs were Grade 2 in intensity and had a soft blowing quality. The intensity of a Grade 3 murmur increased to Grade 6 after the intravenous administration of 2 mg of phenylephrine HCl (Fig. 4). In addition it became musical in early diastole and in presystole while retaining its noisiness in mid-diastole. A prominent band lesion was found on the left coronary cusp of this horse at post-mortem examination. A band lesion was found on cusps of the aortic valve in 8 of the 11 horses and mules which had a noisy diastolic murmur.

Other considerations. The loud musical murmurs radiated over a wide area on the thoracic surface thereby making their localization difficult. The softer musical murmurs were localized at the second sound area or the left third or fourth intercostal space 3 to 4 inches dorsal to the point of the olecranon. In spite of their softness the noisy murmurs could be heard readily over an area extending 1 to 3 inches caudad and ventrad to the second sound area.

With two exceptions a distinct precordial thrill was present in all horses and mules which had a musical murmur. A thrill was present in only 2 of the animals which had a noisy murmur.

The frequency response of the intra-cardiac transducer used in the catheterization procedure in one horse enabled the instrument to respond to vibrations of the musical murmur that was present (Fig. 6). Some vibrations sensed by the intra-cardiac transducer and displayed on the pressure tracing were comparable to those sensed by the microphone on the chest wall. The

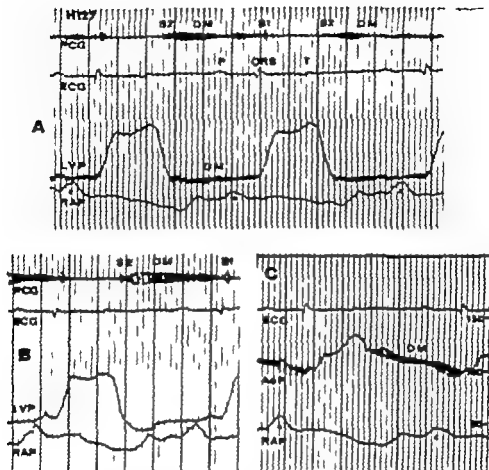


Fig. 6 (phonocardiogram (PCG) electrocardiogram (ECG) left ventricular pressure (LVP) aortic pressure (AP) and right ventricular pressure (RV) recorded from a horse with a diastolic murmur (DM) of aortic insufficiency. Tracings obtained by intra-arterial transducers. Aortic pressure (C) recorded greater in mmHg than left ventricular pressure (L and B). Only the aortic pressure standardized expressed in millimeters of mercury. In A vibrations of the diastolic murmur are superimposed upon the left ventricular pressure tracing. Transducer located in left outflow tract. In B as the transducer is positioned deeper in the ventricle vibrations disappear from the pressure tracing. In C the tone of the diastolic murmur (DM) are superimposed upon the aortic pressure tracing, when the transducer is positioned near the aortic valve. (Trac) total acceleration of the murmur commences near the peak of the right ventricular wave (a).

murmur was recorded best when the transducer was near the aortic valve. Movement of the transducer in either direction from the aortic valve resulted in progressive diminution of the vibrations of the murmur on the pressure tracing.

Fluctuations related to atrial systole were present in the aortic pressure tracings of 2 of the 3 horses catheterized (Figs. 3 and 4). Praxystolic accentuation of the murmurs occurred during the course of these atrial waves.

Discussion

The presence of a band lesion on a cusp of the aortic valve of the hearts of 18 of

21 horses and mules which had a diastolic murmur was indicative of the importance of that lesion in causing aortic insufficiency in those species. A comparable lesion was absent from the hearts of 13 horses and mules which had no diastolic murmur. Eversion of the free edge of those aortic cusps afflicted with a band lesion was usually apparent when the aortic valve was viewed from the root of the aorta. Further evidence that bands resulted in insufficiency was gained by sliding a finger from the base to the free edge on the aortic surface of the affected cusp. The edge of the cusp distal to the band would exert rather than catch the finger as did a

normal cusp. Apparently the band acted as a stricture in preventing the cusp from billowing out in a manner necessary for maintenance of competency of the valve. The fact that jet lesions were found opposite and ventral to a cusp with a band lesion in most cases was more conclusive evidence that band lesions resulted in insufficiency. Significant band lesions were absent from the aortic valves of 3 horses which had a noisy diastolic murmur. Small nodules on the aortic valves of those horses could have resulted in slight insufficiency. Insufficiency was considered to be probable in 3 horses whose hearts were not examined post mortem. This probability was based on the observation that the murmurs in these were comparable to the murmurs in animals proved to have aortic insufficiency.

It is stated that the generation of a musical diastolic murmur is dependent upon the flow of blood past a structure capable of vibrating freely in a periodic manner.¹ Sagging and eversion of an aortic cusp usually the right anterior one is a common cause of musical diastolic murmurs in man.¹² It has been reported that the presence of bands on an aortic cusp leads to eversion of the cusp and the consequent generation of a musical diastolic murmur in man.¹³ An everted aortic cusp was probably the source of the musical diastolic murmurs in our study since postmortem examination in each case revealed the presence of a band lesion which appeared to permit eversion of the cusp. Why the murmur was noisy in other instances in which an everted cusp was the apparent cause of insufficiency is not immediately evident. Perhaps in some of these the murmur was musical at one time but because of a progressive change in the valvular lesion the murmur became noisy. The amount of regurgitation, the position of the everted cusp relative to the regurgitant stream, and the thickness and width of the everted edge are factors which probably enter into determining whether the murmur is musical or noisy and its frequency if musical.

Jet lesions have received consideration as a site for the production of murmurs. It is theorized that the roughened surface of the jet lesion is capable of generating audible vibrations as a consequence of the impact of a regurgitant stream of blood.

It might be significant that the septal jet lesions of 3 horses which had a sea gull type of murmur were composed of cusp-like ridges oriented toward the aortic valve (Fig. 2). No jet lesion was found in another horse which had a comparable murmur, however.

Presystolic accentuation was one of many interesting features of the musical murmurs. In man a diastolic murmur of pure aortic insufficiency that is accentuated in presystole is referred to as an Austin Flint murmur.^{10,11} It is believed that the regurgitant stream of blood from the aortic valve strikes the anterior cusp of the mitral valve and displaces it into the stream of blood coming from the contracting atrium. By being subjected to two opposing streams of blood the anterior cusp of the mitral valve is considered to vibrate and thereby generate the audible vibrations of the Flint murmur.

An everted aortic cusp was considered to be the origin of both the early diastolic and the accentuated presystolic musical murmurs in the horse and mules studied for the following reasons: (1) Presystolic accentuation of the murmur occurred in the absence of jet lesions on the anterior cusp of the mitral valve of some horses. In these jet lesions on the ventricular septum indicated that insufficiency was not a recent development. From this the importance of the anterior cusp of the mitral valve as the site of origin of the accentuated presystolic murmur of horses becomes open to question. (2) Localization of a musical murmur (accentuated presystolic element included) at the aortic valve by an intracardiac transducer in one horse (Fig. 6) indicated that the everted left coronary cusp found at necropsy was the origin of both the diastolic and presystolic murmur in that particular case. (3) A presystolic musical murmur was never present unless preceded by an earlier musical murmur suggesting a common site of origin for the two. It seems to be likely that if the presystolic musical murmur had as its origin some vibrating structure other than an everted aortic cusp there would be instances in which the murmur is noisy in early and mid diastole and musical in presystole.

It is apparent that at the time of atrial systole the character of the musical mur-

cent NaCl in distilled water) solution. The lobe was immersed in a saline filled bottle which was then sealed (Fig. 1). The four cannulas were connected with pipes which passed through the rubber stopper of the bottle with care taken so that the entire system was free of air. The perfusion pressure gradient was the drop in pressure in centimeters of saline from the fluid level of the pulmonary arterial reservoir to that of the venous reservoir. Vascular conductance was calculated as the flow in liters per minute per centimeter of saline of the arteriovenous pressure difference. Moment to moment displacement of fluid from or into the airway or pleural spaces was indicated by movement of a fitted plastic bull marker in horizontal tubes connected with the bronchial or pleural apices. Airway and pleural pressures were held constant by means of syphons and overflow reservoirs to which they were connected. The transpulmonary pressure was established by setting the level of the pleural pressure at either 2.5 or 4 cm below the airway pressure level. The pulmonary venous outflow was measured with a graduated cylinder and stopwatch. Other details have been described.¹

The data obtained included the empty

wet weight of the lung lobe under study, the levels of the reservoirs attached to the arterial, venous, airway and pleural connections, the rate of flow through the vascular system, and the rates of movement of fluid into or out of the airway and pleural compartments.

Studies were made of the effect of (1) variations in arterial pressure as the venous pressure was held constant; (2) equal changes in both arterial and venous pressure levels, thus holding the arteriovenous pressure difference constant; and (3) variations in venous pressure as the arterial pressure was held constant.

Results

Analysis of the results on the three series of experiments revealed that all of the accumulated data, which at first sight appeared to be dissimilar, could be treated in a consistent and comparable manner by considering the airway pressure to be the zero reference level (Fig. 2). The data are analyzed in terms of whether conductance was zero, basal, intermediate or maximal.

Zero conductance. Flow and conductance were zero in all tests in which airway pressure exceeded both arterial and venous pressures (Fig. 3). Since there was no flow

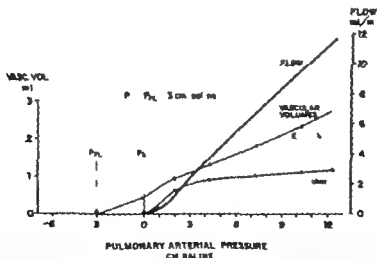


Fig. 2. Effect of vascular pressure on vascular volumes and flow. Values are per gram of empty wet lung lobe. The pressure in the arterial reservoir is given in the horizontal axis. Airway pressure (P_n) is the zero reference. In the experiment shown, venous and pleural pressures are both set at 3 cm below airway pressure. Vascular volumes are given in the vertical axis on the left. Extralobar vascular volume shows an increase in volume when arterial pressure exceeds pleural pressure as indicated in the upper right line. The lower right line gives the intralobar vascular volume as arterial pressure is raised. Flow is given in milliliters per minute in the right vertical axis and in the heavy line. Discussed in text.

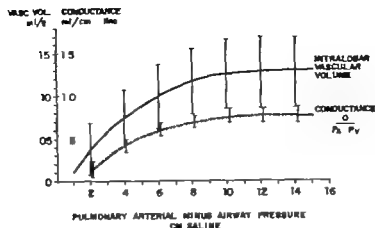


Fig 3 Relationship between intralobar vascular volume and vascular conductance ($P_A > P_{TV}$). In this set of experiments on wet dogs mean values are given by the curves and standard deviations by the vertical lines. The scale on the left of the vertical line is vascular volume in milliliters per gram of lung lobe. The scale on the right of the vertical line is conductance in milliliters per minute per centimeter of saline. The horizontal axis is the height of the pulmonary arterial pressure above airway pressure in centimeters of saline.

despite an arteriovenous pressure gradient the absence of a functioning communicating channel between the arterial and venous reservoirs was indicated. As long as the arterial reservoir remained lower than the airway reservoir there was no displacement of fluid from the airway.

Basal conductance. As the arterial pressure was raised slightly above the airway pressure a rapid movement of the indicator ball in the horizontal tube connected to the bronchus showed that fluid was displaced from the airway compartment and flow through the vascular bed began. The indicator ball came to approximate rest within 1 minute after the alteration in the arterial pressure. When the arteriovenous pressure difference and the airway pressure were held constant for 20 minutes or more the rate of flow also remained constant.

When venous pressure was lower than pleural pressure oscillations of the entire system with a recurrence rate of 1 to 3 per second were observed. The oscillations stopped when venous pressure was raised to pleural pressure; conductance increased slightly at this time.

Intermediate conductance. When pulmonary venous pressure was negative progressive elevation of the arterial pressure above zero displaced fluid from the airway and conductance increased above basal values. At an arterial pressure of about 7

cm of saline an amount of fluid equal to about 14 per cent of the empty wet weight of the lung lobe was displaced from the airway (Figs 2 and 3).

Maximal conductance. When arterial pressure was more than 7 cm of saline above airway pressure and venous pressure was more than 4 cm of saline above airway pressure additional elevations of arterial pressure up to 13 cm of saline had no further effect on the displacement of fluid from the airway or on the conductance (Fig 3). Flow increased approximately linearly with the arteriovenous pressure difference. At arterial pressures higher than 13 cm of saline fluid was displaced from the airway at a continuous rate. At 15 cm of saline the continuous rate of displacement became very rapid.

Relationship between airway displacement and vascular conductance. Vascular conductance increased in direct proportion to the volume of fluid displaced from the airway (Figs 3 and 4). Conductance was increased as the venous pressure was elevated above airway pressure until venous pressure was 4 cm of saline; further elevations of venous pressure had no effect on conductance.

In some experiments arterial pressure was held constant while venous pressure was elevated by increments from subpleural pressures (Fig 4). When venous

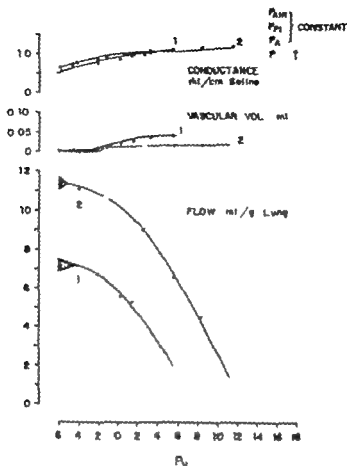


Fig 4 The effects of the transpulmonary pressure on flow rate, intralobar vascular volume, and conductance. Flow rate per minute is given in the lower curve, labeled ml/g. Conductance is given in the upper scale. Intralobar displacement per gram of lung on the middle vertical scale. Pressures were held constant in the pulmonary artery and in the airway and pleural spaces. In experiment 1 $P_A = 7.0$ cm of water, and $P_{PL} = 3.5$ cm of water. In experiment 2 P_A was 12.0 and P_{PL} was -3.5 cm. Intralobar vascular pressure (P_v) is given in the horizontal axis. When pulmonary venous pressure was -6.0 cm, the plethysmographic indicators and entire lung lobes showed oscillations (flutter) with a recurrence rate of 116 per minute in experiment 1 and rate of 108 per minute in experiment 2. The oscillations are indicated by the widened line. The oscillations ceased when venous pressure was raised to the pleural pressure level. With further increments in pulmonary venous pressure, intralobar vascular volume increased and flow rate decreased in accord with the decreased arteriovenous pressure gradient. Flow approached zero as venous pressure equaled arterial pressure; the conductance and fluid displacements were maximal at this level as the intralobar vascular volume reached almost steady levels. Vascular conductance varied with the intralobar vascular volume. The volume entering the intralobar vessels was less than in Figs 2 and 3 since the intralobar vessels were already partially opened by the high pulmonary arterial pressures. The increases in intralobar vascular volume in experiment 1 were greater than in experiment 2. Intralobar vascular volume effects are not given.

pressure was less than pleural pressure oscillations of the entire system were observed and conductance was small. As pulmonary venous pressure was raised the oscillations ceased, an increment in displacement of fluid from the airway compartment was observed and conductance approached maximal values. When the displacement of fluid from the airway be-

came maximal conductance also became maximal.

The rate at which the conductance changed as filling of the intralobar vessels took place is illustrated in Fig 5. In these experiments some of the parameters were held constant while others are changed. In the upper line the arteriovenous pressure gradient, the airway pressure, and the

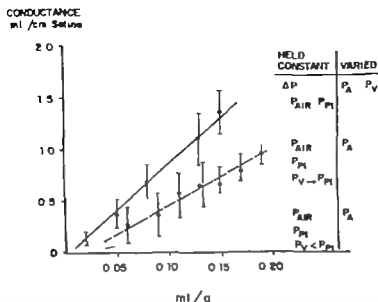


Fig. 5. The relation ship between intralobar vascular volume and conductance. The vertical axis gives conductance in milliliters per minute per centimeter of saline; the horizontal axis gives intralobar vascular volume in milliliter per gram of lobe. In the upper line the vascular pressure was increased by the simultaneous increase in arterial and venous pressures, maintaining a constant arteriovenous pressure gradient of 3.0 cm H₂O. In the middle line the arterial pressure was increased while airway and pleural pressures were held constant; venous pressure was raised to, and the pleural pressure level. Similar conditions held in the lower line except that venous pressure was held constant at 3 cm or more below the pleural pressure. In all experiments vascular conductance increased with intralobar vascular volume. However the effect varied with the level of the venous pressure. Conductance was maximal when venous pressure exceeded airway pressure. The dots on the two sets of upright lines represent mean values. The vertical lines give the standard deviations.

pleural pressure are all held constant. The arteriovenous pressure difference is held constant by varying the arterial and venous pressures by equal increments. As arterial and venous pressures are raised the volume displaced from the airway (milliliters per gram) is directly proportional to the conductance. This effect varies with the level of the venous pressure.

In the middle line of Fig. 5 airway, pleural and venous pressures are held constant. Venous pressure was slightly less than or equal to pleural pressure; only the arterial pressure was varied. The displacement from the airway varied directly and in a linear manner with the conductance with a reduced slope.

The dashed line gives data obtained when airway, pleural and venous pressures are held constant; venous pressure is lower than pleural pressure. Increases in the arterial pressure were associated with displacement of fluid from the airway with changes in conductance.

The solid dots in Fig. 5 represent mean values obtained in the six experiments. The vertical lines represent the standard deviations of the conductance as volume was displaced from the intralobar compartment.

Effect of transpulmonary pressure. The effects of intralobar volume and of the resulting geometric effects on the pulmonary vasculature were examined by lowering the pleural pressure from -2 to -40 cm (Fig. 6). The increase in transpulmonary pressure was associated with enlargement of the extralobar vascular volume in accord with the greater transmural pressure acting on the extralobar vessels. Conductance was not affected.

Discussion

The results are discussed in terms of varying levels of vascular conductance and in terms of the mechanical forces which affect conductance.

Zero conductance. The absence of flow despite a drop in pressure from the arterial

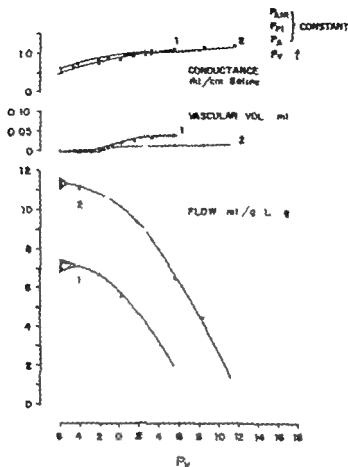


Fig 4 The effects of the transpulmonary pressure on flow rate, intralobar vascular volume and conductance. Flow rate per minute is given in the lower vertical axis labeled ml/g. Conductance is given in the upper scale. Intralobar displacement per gram of lung on the middle vertical scale. Pressure were held constant in the pulmonary artery and in the airway and pleural spaces. In experiment 1 $P_A = 7.0$ cm of saline and $P_{PL} = 3.5$ cm of saline. In experiment 2 P_A was 12.0 and P_{PL} was -3.5 cm. Pulmonary venous pressure (P_v) as given in the horizontal axis. When pulmonary venous pressure was -6.0 mm the pleural indicators and entire lung lobe showed oscillations (flutter) with a recurrence rate of 116 per minute in experiment 1 and a rate of 108 per minute in experiment 2. The oscillations are indicated by the widened line. The oscillations ceased when venous pressure was raised to the pleural pressure level. With further increments in pulmonary venous pressure intralobar vascular volume increased and flow rate decreased in accord with the decreased arteriovenous pressure gradient. Flow approached zero as venous pressure equaled arterial pressure; the conductance and fluid displacements were maximal at this level as the intralobar vascular volume reached almost steady levels. Vascular conductance varied with the intralobar vascular volume. The volume entering the intralobar vessels is less than in Figs 2 and 3 since the intralobar vessels were already partially opened by the high pulmonary arterial pressures. The increases in intralobar vascular volume in experiment 1 were greater than in experiment 2. Extralobar vascular volume effects are not given.

pressure was less than pleural pressure oscillations of the entire system were observed and conductance was small. As pulmonary venous pressure was raised the oscillations ceased an increment in displacement of fluid from the airway compartment was observed and conductance approached maximal values. When the displacement of fluid from the airway be-

came maximal conductance also became maximal.

The rate at which the conductance changed as filling of the intralobar vessels took place is illustrated in Fig 5. In these experiments some of the parameters are held constant while others are changed. In the upper line the arteriovenous pressure gradient, the airway pressure and the

As the arterial pressure increased above the airway pressure a small volume of fluid was displaced from the airway compartment and flow began. The displacement can be accounted for as a slight filling of the intra-alveolar capillaries. If all the capillaries in a lobe were identical all the vessels would be slightly opened.

Maximal conductance When the displacement of fluid from the airway is maximal as at arterial pressures of 7 cm or more of saline conductance becomes maximal. It may be assumed therefore that this pressure is sufficient to fill the capillaries of the alveolar spaces. In this range of fully filled vessels the linear relationship between perfusion pressure and flow shows that the Hagen-Poiseuille law originally developed for flow through glass tubes applies to the pulmonary capillaries. Since further elevations of arterial pressure up to 13 cm of saline have no effect on conductance it may be assumed that filled alveolar capillaries are nondistensible within this range of pressure. This suggests that the capillary structure is supported by sufficient material to prevent stretching at least up to a transmural pressure of 13 cm of saline. The previously reported sudden increase in the rate of displacement of fluid from the airway when arterial pressure exceeds 13 cm of saline² suggests that ballooning has occurred and that a threshold to filtration may have been breached presumably by some fundamental change in the characteristics of the capillary wall. These findings also indicate that the use of transmural pressures as high as 15 cm of saline applies abnormal stresses to the pulmonary vessels² and may introduce significant artefacts.

Intermediate conductance Conductance varied with the volume of fluid displaced from the airway compartment and with the presence of oscillations in the system. At intravascular pressures slightly higher than airway pressure the capillaries apparently open partially and flow begins. Further increments in vascular pressure up to 7 cm of saline displace more fluid from the airway presumably as a result of the passive filling of the intra-alveolar capillaries. Conductance increased with the opening of the vessels as indicated at the point of maximal displacement of fluid from the airway (Figs

3 and 5). The close relationship between displacement and conductance is indicated by the fact that both factors reached maximal values at the same time.

Pressure-flow interrelationships Nonflow experiments showed a maximal displacement from the airway at an intravascular pressure of 4 cm of saline.¹ The displacement in the flow experiments was considerably reduced and seemed to vary with arterial venous and airway pressures and with the rate of flow (Figs 5 and 6). These effects could be attributed at least in part to the likelihood that in flow a portion of the total energy becomes manifest as velocity or is lost as a result of friction. Because of these losses of pressure the capillaries are not completely filled and conductance is less than maximal until the arterial pressure is above 7 cm of saline.

As stream velocity increases the fall in intravascular pressure may lower the transmural pressure to zero and thereby result in collapse of the vessel. With collapse velocity becomes zero, intravascular pressure rises sharply and redistends the vessel so that flow begins again. As the stream velocity increases the conditions for closure are again established and a recurrent cycle of opening and closing (flutter) of the vessel is generated. Conductance varies during each cycle from a maximum when the vessel is completely open to a minimum of zero when it is closed. Opening and closing in phase of all vessels of the lung lobe produces marked oscillations of the system. The flow and the calculated average conductance increase with the proportion of the time that the vessel is open (duty cycle). In the lungs if physical considerations collapse occurs at the site of the lowest transmural pressure, at the downstream segment of the collapsible vessel. It latter is probably more likely to occur in intralobar (alveolar) vessels since transmural pressure is lower in the vessel of the airways than in the vessel facing the pleura. Recurrent opening and closing of the pulmonary capillaries of the rabbit lung originally observed by Weirauch and associates¹⁴ has been confirmed by numerous other workers. Diffusion studies in patients and in the isolated lung bed led Lewis and co-workers¹⁵ to state that

capillary segments may be open or closed.

Arterial pressure. An elevation in arterial pressure and inflow also raises the pressure throughout the system. When the rise is sufficient to increase the transmural pressure at the downstream end of the capillary to positive values, vascular collapse is inhibited and conductance becomes maximal.

Venous pressure. Elevation of the pulmonary venous pressure sometimes results in an increase in pulmonary vascular conductance. In previous studies^{14, 15} this laboratory has indicated that this may result from the more complete filling of previously collapsed vessels. When the vessels are partially collapsed, elevation of the venous pressure raises the intravascular pressure and produces a more positive transmural pressure which rounds out the vessels, inhibits slitter and increases vascular caliber and conductance to a maximum.

Similar effects of increasing flow associated with an elevation of the downstream pressure have subsequently been noted in systemic vascular beds by Burton¹⁶ and for the pulmonary bed by Lloyd,¹⁷ Borst,¹⁸ Carhill,¹⁹ Brinister,²⁰ Haddy, and Campbell²¹ and their co-workers. These workers did not measure the concomitant changes in vascular volume.

When the pulmonary capillaries are fully distended and conductance is maximal, further increases in arterial or venous pressures or in flow have no further effects on vascular conductance.

Blood flow. Increases in pulmonary blood flow in the air-filled lung are known to increase the pulmonary arterial pressure only slightly, a response usually attributed to an active dilatation of the pulmonary vasculature. It is suggested that the increase in conductance may represent the passive opening of previously collapsed alveolar capillaries in the more elevated segments of the lung. Thus a very slight rise in intravascular pressure can open many new channels and enhance pulmonary vascular conductance without invoking smooth muscle relaxation.

Airway pressure. Factors which affect airway pressure even slightly may play an important role in the regulation of pulmonary vascular conductance.²² In the absence of ventilatory movements, airway pressure

remains constant at atmospheric pressure. During normal ventilation the intralobar pressure oscillates over a range of a few centimeters of saline. These small changes in pressure can determine whether at a given moment the transmural pressure of some of the capillaries in the air-filled lung is positive and conductance and volume are maximal or whether the transmural pressure is negative and the collapsed capillaries provide zero conductance. Thus the elevated airway pressure in expiration may be considered to collapse vessels and decrease conductance. Larger variations in airway pressure are developed during dyspneic breathing and coughing.²³

Effect of gravity. In the air-filled lung the transmural pressure tends to be more positive in the more dependent portions than in the more elevated portions. The dependent portions therefore have higher vascular conductances and flows. In an air-filled lung, an increase in airway pressure as occurs in expiration can generate a wave of collapse of the capillaries which sweeps from the more elevated to the more dependent capillaries of the lobe. In the present preparation hydrostatic effects are eliminated and all capillaries probably open and close together. This technique eliminates the wide spectrum of the degrees of openness or collapse of the intralobar vessels observed in the air-filled lung. As a result small differences in pressure produce relatively large effects on conductance.

The changes in conductance given above have generally been explained as being due to either vasodilation or to distention of the caliber of the pulmonary vessels. Borst¹⁸ observed that the change in conductance is less notable when arterial or venous pressure is high. Haddy²⁰ and Rodbard¹⁶ have shown that the effect is most marked when the pulmonary venous pressure approaches airway pressure. The present results indicate that conductance changes in the caliber of the capillaries varies with transmural pressure. These effects are remarkably similar to those exhibited by a soft-walled paravascular collapsible tube.^{24, 25}

As transmural pressure became progressively less positive as by a lowering of venous or arterial pressures, or a raising of airway pressures, fluid was displaced into the airway, indicating partial collapse of

the pulmonary capillaries and conductance was reduced. Under these circumstances conductance increased with small increases in venous or arterial pressure or reductions in airway pressure (Figs. 2 and 3). These effects might be misinterpreted as a vaso-dilator response although mechanical effects at the collapsible capillary can readily account for them.

The foregoing analysis clarifies the definite but limited effects on conductance of changes in arterial, venous and airway pressures and of flow. It is suggested that these effects on conductance are determined ultimately by their hydrodynamic effects on the cross sectional area of the capillary bed.

The present data support the concept that capillary transmural pressure determines the effective cross sectional area and conductance of the vascular bed in the lung as well as in other structures.³

Summary

Vascular conductance (flow rate per unit of arteriovenous pressure gradient) was studied in the degassed lung lobe in which saline solution was used to fill the airway and the pleural space and to perfuse the blood vessels at selected arterial and venous pressures. This preparation eliminated effects due to surface osmotic and hydrostatic forces, those due to geometric relationships resulting from distention of the lung and those which result from oscillations of pressures in the airway and in the vessels.

All the data obtained could be treated in a consistent manner by considering the airway pressure to be the zero reference level. The phenomenon of critical closing could be demonstrated as a mechanical effect due to negative transmural capillary pressure; thus when airway pressure exceeded arterial and venous pressures conductance was zero. As arterial pressure was raised above airway pressure fluid was displaced from the intralobar (airway) compartment. Conductance was correlated directly with the volume of displacement of fluid from the intralobar compartment. These data indicated that intralobar vessels presumably the alveolar capillaries opened when transmural pressure was positive and closed when it was negative.

Variations in conductance occurred with changes in transmural pressure. Positive transmural pressures were produced by elevations of arterial or venous pressures or by a lowering of airway pressures. When intralobar capillary transmural pressure was about +7 cm of saline conductance was maximal.

Changes in the degree of filling of the lung lobe or in the volume of fluid in the vessels exposed to the pleural surface had no significant effects on conductance.

Recurrent oscillations of the system were observed at transmural pressure of approximately zero. These oscillations were similar to the patterns of recurrent closure and opening of soft walled vessels (flutter) noted in previous studies. Conductance was proportional to the period during which the vessel was open (duty cycle).

It is shown that marked changes in pulmonary vascular conductance can be produced by mechanical effects at the collapsible intra-alveolar capillary. Before changes in conductance can be attributed to humoral neurogenic or pharmacologic factors the potential mechanical effects on conductance of changes in transmural pressure at the capillary must be controlled.

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Pulmonary angiography in experimental pulmonary embolism

James E. Dalen MD*

Virendra S Mathur MD**

Hilary Evans MD***

Florence W Haynes PhD

Ali A Par Shahriari MD****

Paul D Stein MD**

Lewis Dexter MD

Boston, Mass

Pulmonary thromboembolism is being increasingly recognized as one of the most common causes of death in the hospitalized population.¹ Effective therapeutic and prophylactic measures are available but their implementation demands accurate recognition of this disorder.

The use of pulmonary angiography as an aid to the diagnosis of pulmonary embolic disease has been recent.

As early as 1932 Lochhead and associates² reported that pulmonary angiography can demonstrate gross abnormalities in the pulmonary vasculature of dogs minutes after they are embolized with autologous blood clot. In 1954 selective pulmonary angiography was used by Atchison and Welch³ to demonstrate pulmonary thromboembolic disease in a patient. Yet it has only been within the past several years that

some investigators^{4,5} have begun to include this technique as an integral part of the diagnostic work up of patients suspected of pulmonary embolism.

The recognition of evidence of thromboembolism by angiography in man is fraught with difficulty. Control angiograms are not available to distinguish possible variations in the normal pulmonary vasculature from abnormalities due to embolism. Angiographic abnormalities due to embolism must be distinguished from abnormalities that are due to the frequently coexistent cardiac and pulmonary disease. The possible changes in the angiographic appearance of sequelae of thromboembolism that may occur with the passage of time are not known.

This study was undertaken to determine the immediate and sequential changes oc-

From the Department of Medicine and Pathology, Peter Bent Brigham Hospital and Harvard Medical School, Boston, Mass.

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* is director of the Division of Cardiology, Peter Bent Brigham Hospital and Harvard Medical School, National Institutes of Health, 121 Mount Vernon Ave., Boston, Mass. 02115.

** Research Fellow supported by the National Institutes of Health, 121 Mount Vernon Ave., Boston, Mass. 02115.

*** Research Fellow supported by the National Institutes of Health, 121 Mount Vernon Ave., Boston, Mass. 02115.

**** Research Fellow supported by the National Institutes of Health, 121 Mount Vernon Ave., Boston, Mass. 02115.

curing in the angiographic appearance of the pulmonary vasculature of the normal dog when pulmonary thromboembolism is induced in such a way that the size and the location of the emboli are known and can be confirmed by postmortem examination.

Methods

Pulmonary embolism was induced in 23 closed chest mongrel dogs weighing from 11 to 20 kilograms (median 17 kg.). Anesthesia was induced by intraperitoneal pentobarbital 32 mg. per kilogram of body weight. The dogs were intubated and ventilated with room air by a Starling pump with a tidal volume of 300 ml. and a rate of 30 respirations per minute.

Six dogs were embolized with autologous blood clot produced by the method described by Lochhead and co-workers.⁸ An 11 cm. to 13 cm. segment of the left external jugular vein was isolated and occluded then 10 ml. of thromboplastin* extract was injected into the isolated vein segment. An average of 3.0 ml. of clot was thus formed and was released after the vein had been occluded for 30 minutes.

Seventeen dogs were embolized with autologous blood clot rendered radiopaque by a modification of the technique of Allison and colleagues.⁹ Four milliliters of Dionosil† 1 ml. of 10 per cent CaCl_2 and 2 ml. of thromboplastin extract in a mixture was added to 9 ml. of autologous venous blood mixed thoroughly and then immediately transferred to a glass tube with an internal diameter of 4 mm. After 60 to 120 minutes at room temperature 2 to 6 ml. of the resultant radiopaque clot was introduced into the left external jugular vein.

Hemodynamic angiographic and radiographic studies were performed before minutes after and at intervals varying from $\frac{1}{2}$ hour to 24 hours after embolization (Table I).

In each control and follow up study pulmonary and femoral arterial pressures were recorded with a Sanborn recorder by means of P23d Statham strain gauge manometers the electrocardiogram (Lead II) was moni-

tored and selective pulmonary angiography in at least two projections was performed for each dog. Target to film distance was held constant by taking each angiogram with the film 2 cm. above the anterior chest. Two hundred and eighty angiograms were recorded and assessed. In the 17 dogs embolized with radiopaque blood clot plain chest x-ray films were taken to identify the location of the radiopaque thromboemboli.

Selective pulmonary angiography was performed by the single film technique. With a No. 6 Rodriguez Alvarez catheter positioned in the main pulmonary artery or the right ventricular outflow tract 1.5 ml. per kilogram of body weight of 75 per cent Hypaque VI* was injected in a Cordis injector at a rate of 30 ml. per second. Angiograms were taken at the peak of the arterial phase of the passage of contrast medium through the pulmonary vasculature.

This technique of angiography allowed identification of all vessels larger than third order arteries using the Edwards¹⁰ and Brenner¹¹ classification of the pulmonary vasculature (Table II).

Immediately prior to sacrifice after the last follow up study in each experiment 10,000 I.U. units of heparin† was given intravenously. The heart and lungs were removed en bloc. The lungs were inflated by introducing saline into the trachea at a pressure of 10 cm. of saline and then in dogs embolized with radiopaque blood clot plain roentgenograms were taken in order to visualize the emboli. In all 23 dogs postmortem pulmonary arteriograms were recorded by the method of Smith and co-workers.¹² This technique allows identification of the elastic arteries and all four subdivisions of the muscular arteries (second order third order lobular and arterial branches) (Table II). The pulmonary vasculature of each lung was then dissected and selected microscopic sections were studied.

Results

I Acute sequelae of experimental pulmonary embolism

*Sample 100 Warr. Ch. Co. Inc. Morris Plains, N.J.
†Dionosil, aqueous. Chas. Lab. rat. res. Ltd. Overdale & Enfield.

*Hypaque VI, am. and isopropyl am. d. salt. and. W. B. Lewis Lab. rat. res.
New York, N.Y.
†Heparin am. and isopropyl am. d. salt. and. W. B. Lewis Lab. rat. res.

Table I Time of follow up studies (hours)

Table 1. Time of junction of embolus											
	Experiment number	Control	Immediate	Hours after embolization							
				1/2	1	2	3	4	6	8	24
Plum clot											
	1		✓		✓	✓					
	2	x	✓	✓	✓	✓	✓				
	3	✓	✓	✓		✓	✓	✓			
	4	x	✓	✓	x	✓					
	5		✓	✓	✓	✓		✓			
	6	✓	✓	x		✓	✓				
Radiopaque clot											
	7	✓			✓			✓			
	8	✓	✓		✓	✓		✓	✓		
	9							✓			
	10	✓	x		✓		✓	✓			
	11	x	✓			✓			✓	✓	
	12		✓		✓						✓
	13	✓	✓			✓					
	14	✓			✓						x
	15	x	x		✓	✓		✓			
	16	x	✓		x	✓		✓			✓
	17	✓	✓			✓					
	18	x	✓			✓					x
	19	✓	x		✓	✓					✓
	20	x	✓			✓					✓
	21	✓	✓			✓					✓
	22	✓				✓					✓
	23	✓									✓

Table II Classification of pulmonary vasculature of the normal dog

	Recognition by perimeter angiogram	Recognition by perimeter microradiogram
Elastic arteries (diameter > 10 mm)		
MPA L1A RPA	+	+
Lobar	+	+
First-order (segmental)	+	+
Muscular arteries (diameter 0.1 to 10 mm)		
Second-order	+	+
Third-order	+/-	+
Arterioles	0	+
Atrial	0	+/-
Arterioles (diameter 0.1 to 0.1 mm)	0	0

See Fig. 2 for further classification of first-order arteries.

DOCUMENTATION OF PULMONARY EMBOLISM BY PLAIN CHEST X-RAY FILMS. In each of the 17 dogs embolized with radiopaque blood clot the opaque clots were clearly seen on plain chest x-ray films taken immediately after embolization. In all 17

dogs emboli were present in both lungs and in most dogs emboli were visible in each lobe of the lungs. There were wide differences in the size of the emboli resulting from the injection of blood clot.

ANGIOGRAPHIC ABNORMALITIES ASSOCIATED



Fig. 1. A normal pulmonary vascular pattern is demonstrated in the control angiogram (left). The plain chest film taken minutes after embolization with 3 ml of radiopaque blood clot (middle panel) identifies numerous emboli in both lungs (bold). The angiogram abnormalities resulting from the presence of these emboli are demonstrated in the angiogram taken minutes later (right). Note the cutoff of the left lower lobar artery with resultant oligemia, cutoff of 1 first-order branch of the right upper lobar artery, and a missing first-order branch of the left upper lobar artery.

ATED WITH THE KNOWN PRESENCE OF EMBOLI IN THE PULMONARY VASCULATURE. The radiopaque emboli noted on the plain films taken immediately after embolization were almost uniformly associated with identifiable abnormalities on the angiograms taken minutes later (Fig. 1).

These angiographic abnormalities were identified by reference to the plain film showing the location of the radiopaque emboli and to the control angiograms taken before embolization. The angiographic abnormalities were the same for the two types of emboli: plain blood and radiopaque blood clot.

Four different angiographic abnormalities were found to be associated with the known presence of emboli in the pulmonary vasculature.

1. Discrete or hazy cutoffs of arteries (Figs. 1, 3, and 8). This was the most common acute angiographic abnormality found to be associated with pulmonary embolization in this study. The arteries most frequently cut off were the first order (elastic) arteries and second order (muscular) arteries. At least two first order arteries were cut off in the angiogram taken immediately after embolization in each experiment.

Cutoffs were less frequent among the larger elastic arteries. Lobar arteries were

cut off in 11 of the 23 experiments. There were no cutoffs of the main right or left pulmonary artery.

With constant reference to the control angiogram, the number of obstructed first order arteries on the angiogram immediately after embolization was tabulated in each experiment. The vascular supply to the seven lobes of the normal dog lung consists of 18 such first order arteries as shown in Fig. 2. These first order arteries supply regions of the dog lung that are analogous to the bronchopulmonary segments of the human lung. If a lobar artery was cut off, the number of first order arteries that it supplied was counted as being cut off. The average number of obstructed first order arteries in the 23 dogs was 6.4 (range 2 to 15). This implies obstruction of at least one third (6.4/18.0) of the pulmonary vasculature. The total degree of pulmonary vascular obstruction would also include the occlusion of smaller arteries supplied by first order arteries that had remained patent.

2. Complete absence of an artery with out a visible cutoff (Fig. 3). In some experiments arteries were occluded near their origin in such a way that they failed to visualize but a cutoff was not apparent. This type of angiographic abnormality particularly when it affected smaller arter-

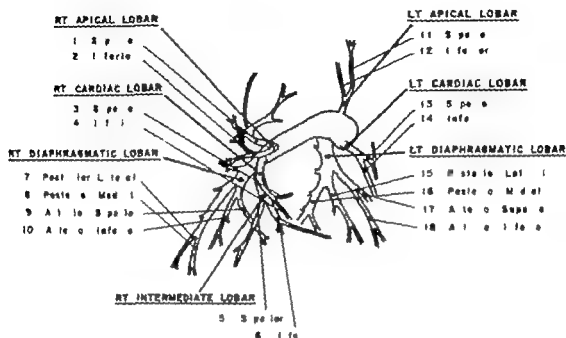


Fig. 2. Classification of arterial supply to normal dog lung (7 lobar arteries 18 first order level). The scheme of the pulmonary arterial tree of the dog in the right anterior oblique projection was defined by one of us (H.E.) on the basis of premortem angiograms correlated with post-mortem arteriograms and dissection. The nomenclature is an extension of that of Edwards and Bremner.

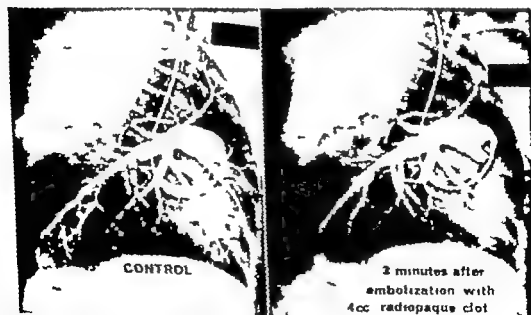


Fig. 3. (left) the control angiogram (left) the left cardiac lobe artery with its two first-order branches. (right) the angiogram taken 3 minutes after embolization of the entire left cardiac lobe artery. About 10% of the point of cutoff cannot be detected in this artery. In the left lower lobe, three first-order arteries are present in the post-embolization angiogram.



Fig 4 In the postembolization angiogram (right) large intraluminal filling defects present in the right lower lobe artery (point of bifurcation in) not present in the control angiogram (left)

ses could be detected only in reference to the control angiogram.

3 Intraluminal filling defects (Fig 4). In dogs embolized with plain blood clot intraluminal filling defects that is negative shadows within the opacified pulmonary arterial tree were at times noted. The subsequent postmortem studies established that the intraluminal filling defects were due to the presence of emboli. Intraluminal filling defects were best visualized in the oblique views and were most frequently noted at points of bifurcation.

4 Areas of oligemia (Fig 5). In the postembolization angiogram in each experiment certain areas of the lung were found to be more radiolucent than the same areas had appeared to be on the control angiogram. In these radiolucent areas fewer small arterial branches were visualized than in the comparable area in the control angiogram. In some cases these areas of oligemia were distal to lobes or first-order or second-order arteries that were cut off. In other cases oligemia occurred without other associated angiographic abnormalities and probably was caused by the obstruction of numerous

vessels that were too small to be individually recognized by angiography. These oligemic areas were most commonly seen in the lower lobes.

ASSOCIATED HEMODYNAMIC EVIDENCE OF PULMONARY EMBOLIZATION. In 21 of the 23 experiments embolization was accompanied by an increase in mean pulmonary arterial pressure of at least 5 mm Hg. For the total group the mean pulmonary arterial pressure increased from an average value of 18.9 mm Hg in the control period to 30.3 mm Hg at 3 minutes after the release of emboli.

EFFECT OF EMBOLIZATION ON SIZE OF MAIN PULMONARY ARTERIES. Angiography provided no evidence of pulmonary vasoconstriction. On the contrary, detectable dilation of major pulmonary arteries almost always appeared on angiograms taken immediately after embolization. The increase in diameter of the main pulmonary artery and its major branches is shown in Table III.

II Serial angiographic and hemodynamic changes after pulmonary embolism. Results of follow up studies.

SERIAL CHANGES IN PLAIN FILM APPEAR

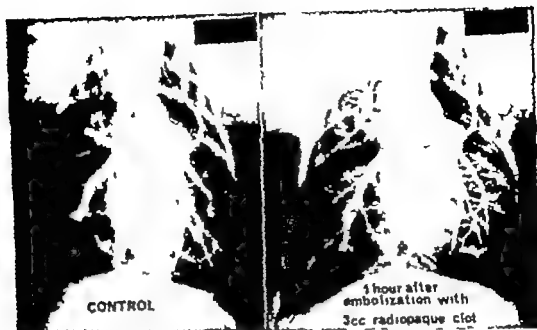


Fig. 5 Comparison of the postembolization angiogram (right) with the control angiogram (left) indicates the presence of oligemic areas in both lower lobes in the postembolization angiogram. In this experiment the areas of oligemia were associated with absent or cutoff of 1-order branches of the lower lobar arteries.

Table III Diameter (mm) of major pulmonary arteries before and immediately after embolization

Vessel	Before (Mean \pm S.E.)	After (Mean \pm S.E.)	t	p value
LA	22.1 \pm .42	21.8 \pm .52	1.0	< .001
LPA	8.9 \pm .23	10.8 \pm .25	6.2	< .001
RPA	11.1 \pm .32	14.0 \pm .71	6.6	< .001

n.s. = difference not significant.

Absence of Radiopaque Clot. In the first 4 hours after embolization with radiopaque blood clot there were few changes in the radiographic size and location of the radiopaque clots. Decreases in the size of the clots was noted in dogs restudied at 24 hours. Fragmentation of the clot emboli as judged by the number of radiopaque emboli visible on the plain x-ray films did not occur after the immediate post-embolization period.

Regression of Angiographic Evidence of Embolism. Each of the four types of angiographic abnormalities found to be associated with the presence of emboli in

the pulmonary vasculature was re-evaluated in the follow-up angiograms.

The most readily detectable immediate angiographic evidence of embolization—discrete or hazy cutoffs of arteries—decreased with the passage of time. For example, Figure 6 (top panel) indicates the mean number of occluded arteries noted at each observation period. The average number of occluded arteries progressively decreased from 6.4 immediately after embolization to 2.8 at 3 to 4 hours after embolization.

The second type of angiographic abnormality—the complete absence of an artery without detectable cutoff (see Fig. 3) also

was quite transient. The majority of these arteries reappeared during the first 4 hours after embolization.

Oligemia is an angiographic manifestation of embolization and is more persistent than cutoffs and absent arteries. Significant decreases in oligemia did not occur during the first 4 hours of follow up. However, of 9 dogs restudied 24 hours after embolization oligemia was detectable in only 3.

Filling defects as sequelae of pulmonary embolization demonstrated a different time course. In most cases filling defects became more apparent with the passage of time. On the immediate angiograms they frequently were subtle and could only be suspected whereas on later angiograms they became more apparent.

SERIAL CHANGES IN HEMODYNAMIC SEQUELAE OF PULMONARY EMBOLIZATION. The

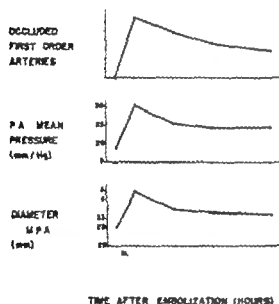


Fig 6. Changes after pulmonary embolization. In these three panels: the number of occluded first order arteries (*top panel*), a average mean pulmonary arterial pressure (*middle panel*) and a average diameter of the main pulmonary artery (*bottom panel*) are plotted for the control, immediate postembolization and the 1 hour, 2 hour and 3 to 4 hour post embolization studies. The maximum number of occluded arteries and the maximum pulmonary arterial pressure and size were noted in the immediate postembolization studies (plotted at 0 hours). By 1 hour after embolization each of these three variables had shown significant returns toward their control values. Additional minimal improvement occurred between 1 and 4 hours after embolization.

average mean pulmonary arterial pressure with respect to time after embolization is plotted in Fig. 6 (*middle panel*). The pressure increased from a control level of 18.9 mm Hg to 30.3 mm Hg immediately after embolization and then decreased to 25.4 mm Hg at 1 hour after embolization with no significant change thereafter to 4 hours.

SEQUENTIAL CHANGES IN SIZE OF MAJOR PULMONARY ARTERIES. The average diameter of the main pulmonary artery is likewise shown in Fig. 6 (*bottom panel*). The progressive return toward normal size after immediate dilation is evident and correlates with the observed sequential changes in pulmonary arterial pressure.

III. Postmortem studies

RESULTS OF RADIOGRAPHIC STUDIES. The postmortem plain x-ray films of the lungs were more sensitive in the detection of small radiopaque emboli than were postmortem plain chest x-ray films. Radiopaque emboli present in vessels smaller than second order arteries could be detected only by the postmortem plain films of the excised lungs.

Postmortem arteriograms reliably demonstrated abnormalities in association with radiopaque emboli visualized by postmortem plain films as illustrated in Fig. 7. Abnormalities on postmortem arteriograms were most easily detected when emboli had caused complete arterial occlusion. Complete embolic occlusion of even the smallest muscular arteries could be recognized. In complete arterial occlusion was more difficult to identify by postmortem arteriography. In these cases filling defects caused by the presence of partially occluding emboli were at times partially obscured by the presence of opaque injection medium surrounding the embolus.

When the pre-mortem angiographic findings were compared to the postmortem arteriographic findings, excellent agreement was found except when emboli were present in arteries smaller than second order. Just as endopaque emboli could not be detected in these small arteries by pre-mortem plain films, abnormalities due to their presence could not be reliably detected by pre-mortem angiography.

In some cases partial embolic occlusion of an artery may be represented as apparent total occlusion by the single film tech-

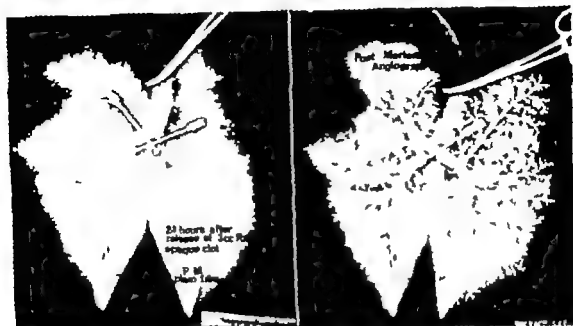


Fig. 7 In the post-mortem plain film (left) numerous radiopaque emboli are present in first-order and second-order arteries, particularly at point of bifurcation. The post-mortem arteriogram (right) demonstrates lack of flow distal to these embolic obstructions.

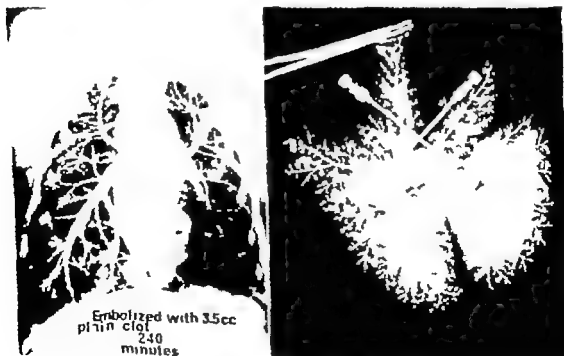


Fig. 8 In the pre-mortem arteriogram taken 4 hours after embolization (left) the left lower lobar artery, cut off just distal to the origin of the cardiac, hilar artery, and there is marked oligemia distal to the clipp. In the post-mortem arteriogram (right) the left lower lobar artery appears to be normal and there is oligemia, however, at the point marked by an arrow, a large partially occluded embolus found in section.

nique of premortem pulmonary angiography. In Fig. 8 a cutoff in the left lower lobar artery with marked distal oligemia is present in the premortem angiogram (left panel). In the postmortem arteriogram (right panel) the left lower lobar artery is patent and there is no distal oligemia. A subtle filling defect is present in the postmortem arteriogram at the point at which the left lower lobar artery was cut off on the premortem angiogram. At dissection a large partially occluding embolus was found at this point in the artery.

RESULTS OF DISSECTION. No clots were found in the right ventricle or right atrium. The largest number of emboli were present in the lower lobes. Smaller numbers of emboli were found in one or more of the other lobes of the lung in each experiment. The arteries most frequently embolized in these experiments were the second order muscular arteries particularly at points of bifurcation.

Of the 9 dogs that were sacrificed 24 hours after embolization evidence of pulmonary infarction was found in only 1 dog.

In the 17 dogs embolized with radiopaque blood clot Dioxonol was found evenly distributed throughout each embolus. There was evidence of clot propagation in only 1 dog.

Abnormalities noted by premortem angiography were invariably associated with corresponding abnormalities in the pulmonary vasculature as found at dissection. There were no false positive findings by premortem angiography. However false negative premortem angiographic findings occurred when emboli were present in arteries smaller than second order. Emboli in these small arteries were not recognized by premortem angiography unless they had resulted in detectable oligemia. All emboli found in second order and larger arteries at dissection were associated with abnormalities on the premortem angiograms.

Discussion

The angiographic abnormalities found to be associated with the presence of thromboemboli in the pulmonary vasculature of dogs (cutoff of arteries, totally absent arteries, intraluminal filling defects, and areas of oligemia) are quite comparable

to those reported in the clinical studies of Simon and Sznachar.¹ They also reported an additional angiographic abnormality,

focal flow decrease, that is a regional decrease in the rate of flow of contrast medium to one or more segments of the lung. This type of abnormality cannot be detected *per se* by the single film technique of angiography utilized in this study. However, as noted above (Fig. 8) in some cases large partially occluding emboli as noted at postmortem examination had appeared as complete cutoffs on the premortem angiograms taken by the single film technique. It is likely that in these cases the angiographic appearance of complete occlusion by the single film technique was a reflection of marked delay in the passage of contrast medium beyond the point of partial embolic occlusion. With the serial film technique of angiography this same partial embolic occlusion might have been represented angiographically as delayed filling of the lung segment distal to the point of partial occlusion. The inability to study specifically the rate of flow of contrast medium to each part of the lungs is the greatest drawback of the single film technique of angiography. By the single film technique delayed filling of a segment of the pulmonary vasculature can be detected only if it is a relatively marked delay. Similarly, asymmetrical prolongation of the arterial phase cannot be detected by the single film technique.

In the follow-up studies reported in this investigation changes in the size and location of thromboemboli were determined by following the size and location of the radiopaque clots by plain chest x-ray films. The reliability of using the radiopacity of these clots as an index of their size has been established by Allison and associates,² who demonstrated in *in vitro* experiments that a decrease in the radiopacity of clots impregnated with Dioxonol is not due to preferential washout of Dioxonol. This was confirmed by our studies in which Dioxonol was found to be evenly distributed throughout each radiopaque clot examined at postmortem.

Few significant changes were noted in the size or location of these radiopaque thromboemboli during the first 4 hours after embolization. However, by 24 hours the

radiographic size of the emboli had decreased by plain chest film. These findings are in agreement with those of Allison and co-workers¹, Bronse and James¹² and Just Viera and Yeager¹⁴.

In contrast to the paucity of observed changes in the size and location of radiopaque emboli during the early follow-up studies significant angiographic changes were noted during this same early follow-up period. The number of obstructed arteries showed a sharp decrease (Fig. 6) and arteries that had failed to visualize in the immediate postembolization angiograms reappeared. This angiographic evidence of resolution of embolic obstruction of the pulmonary vasculature correlated well with the observed decreases in the mean pressure and diameter of the pulmonary artery over the same period of time (Fig. 6).

Similar angiographic evidence of resolution of thromboembolism has been observed in man by Sautter¹⁵, Simon and Sasahara¹ and Alexander and associates⁷.

Summary and conclusions

Comparison of selective pulmonary angiograms in two or more projections taken before and immediately after embolization of healthy dogs with known amounts of autologous blood clot indicated that four different angiographic abnormalities are associated with the presence of pulmonary thromboemboli. Two abnormalities were recognized with relative ease: intraluminal filling defects due to the presence of clot and discrete cutoffs of arteries. The other two angiographic abnormalities, areas of oligemia and total absence of arteries with out a visible cutoff, could most reliably be detected by comparing the postembolization angiogram with the control angiogram.

In follow-up studies angiographic and hemodynamic evidence of resolution of thromboembolism (a sharp decrease in the number of obstructed vessels and a return of pulmonary arterial pressure and the size of the pulmonary artery toward normal values) was noted within 4 hours of embolization. The angiographic and hemodynamic improvements observed during this early follow-up period were far greater than the changes observed in the size and

location of the thromboemboli over the same period of time.

At postmortem the greatest number of emboli were found in the lower lobes especially at points of bifurcation in second order (muscular) arteries. The postmortem findings were quite comparable to those in pulmonary embolic disease in man.

The reliability of this technique of angiography in detecting pulmonary thromboemboli was assessed by comparing the pre-mortem angiographic findings with the findings of postmortem arteriography and dissection. There were no false positive findings by pre-mortem angiography. False negative angiographic findings frequently occurred when thromboemboli were located in arteries smaller than second order. Embolization of these small arteries could be detected only if their obstruction had caused angiographic evidence of oligemia.

The difficulty in detecting subtle angiographic changes without the use of control angiograms, the uncertainties in the detection of embolization of small pulmonary arterial branches and the observed early angiographic improvement that occurred even though thromboemboli were still present in the pulmonary vasculature all suggest that pulmonary angiography in clinical studies may tend to underestimate rather than overestimate the abnormalities due to pulmonary thromboembolism.

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Case reports

Electrocardiographic changes in lightning stroke

C D Burda MD
Shreveport La

Lightning is a brief atmospheric discharge of highly damped electrical current with enormous energy.¹ Although its effects upon the human body are generally similar to those observed in household electrical and high voltage wire accidents the local tissue burns and destruction are usually not so mutilating and severe. Also various neurological, ophthalmic, auditory, pulmonary, and psychiatric complications and sequelae are seemingly more common in survivors of lightning strokes. Sudden death is caused by paralysis of the respiratory center, ventricular fibrillation, cardiac arrest, or any combination of these events; however, survival after prolonged apnea with the aid of vigorous cardiac resuscitative and hypothermic measures has been reported.²

Electrocardiographic changes have rarely been reported in the victims of lightning stroke who were merely stunned or rendered temporarily unconscious. These findings have been patterns of myocardial infarction in three instances^{3,4} and subepicardial injury and ischemic changes in one case.⁵ There was no clinically evident cardiac dysfunction or sequelae. Arrhythmias such as atrial and ventricular fibrillation also may be seen in more severe cases.⁶ Because of the rare opportunity to observe serial electrocardiographic changes in the lightning stroke phenomenon and the absence of such reports in the American and English literature it was

deemed to be worth while to make this case report and review of the literature.

Case report

A 14 year-old Negro male caddy was struck unconscious on the golf course by a discharge of lightning while seeking shelter under a tree during a thunderstorm. Ten to 15 minutes elapsed before the golfers noticed that he was lying on the ground. At this time he was unconscious, oriented, moved all extremities and complained only of mild abdominal pain. There was no past history of heart disease or serious illnesses.

Four physical findings 1½ hours later at the time of admission to the hospital were limited to the skin and abdomen. First and second-degree burns were found on the left scapula, the left flank and left lateral thigh. The abdomen was slightly distended and diffusely tender with hypoviscous bowel sounds. Blood pressure and pulse were normal, likewise heart and lung examinations were unremarkable.

Abdominal x-ray films showed a mild edynamic ileus whereas the chest film was within normal limits. Complete blood count showed a moderate leukocytosis with leftward shift. The differential leukocyte count showed normal neutrophils, blood sugar and serum electrolytes were within normal limits. SGOT and SGPT values were 36 and 16 units respectively (normal above 8-10 and < 35 units). Hematocrit was normal after 24 hours of treatment with nasogastric suction and intravenous fluid.

Twelve serial electrocardiograms of 6-seconds taken over a subsequent period of 12 months are shown in Figs 1 and 2. The first was taken approximately 36 hours after admission on Aug 11, 1964 and revealed a normal sinus rhythm at 60 per minute. P-R interval of 0.14 sec, QRS duration of 0.08 sec and a markedly prolonged QT interval of 0.46 to 0.67 sec (QT of 0.33 sec). The P waves were generally low and notched. The T waves were deep, inverted in Leads II, III, aV, V₁, V₂ and upright

next 2 weeks marked T wave inversion occurred in the precordial leads and in Lead I. These changes were accompanied by prolongation of the Q-T interval and a striking axis shift. These abnormalities improved remarkably within 8 months and the electrocardiogram became normal within approximately 12 months. The development of the notched (Fig 1 Aug 18 1964) although not abnormally wide or tall P waves and diphasic P in Leads V_1 and V_2 (Fig 2 Aug 18 1964) in this case is interesting and might be taken as evidence for some atrial enlargement or injury.

A primary electrical injury or burn of the myocardium by the lightning is a reasonable explanation for the electrocardiographic changes observed in this and other such cases since necropsy studies of a few cases have revealed epicardial hemorrhages⁸ and a peculiar spiral malformation of the myocardial fibers.⁹ In other instances^{10,11} gross and microscopic myocardial abnormalities have been absent or insignificant. Similarly in AC shock and counter shock defibrillation experiments on dogs evidence of fibrous epicarditis subepicardial venous thrombosis and muscle fiber necrosis has been found.¹ Such changes are known to produce subepicardial ischemic T wave changes and vectors.¹² Also patterns similar to myocardial infarction T wave in various atrial and ventricular fibrillation and ventricular tachycardia have been experimentally produced in animals with electric currents.¹³

The interpretation of patterns of infarction in cases of lightning stroke as being synonymous with coronary occlusion should be viewed with caution since it is known that various other conditions without coronary thrombosis such as pericarditis myocarditis cerebrovascular disease¹ pulmonary embolism pancreatitis electrolyte imbalance and ventricular hypertrophy among others may produce identical electrocardiographic changes.¹⁴ Primary myocardial damage from the lightning without coronary involvement is a more likely explanation for these electrocardiographic patterns although the precipitation of a true myocardial infarction by the stress and trauma of the lightning bolt in

an older patient with coronary artery disease could conceivably occur.

It has been postulated that the discharge of lightning simultaneously causes arrest of the respiratory center violent ventricular systolic contraction and shock. This is followed by slow ventricular relaxation and resumption of the cardiac beat however the apnea and resulting anoxia induce a secondary cardiac arrest which then leads to death. Severe and unpredictable electrocardiographic abnormalities might thus result from either myocardial anoxia or possibly from stimulation of the central nervous system via sympathetic storms.¹⁵ Finally no gross derangement in serum electrolytes was found in this case which would exclude an electrolyte imbalance as a cause of these electrocardiographic changes.

Summary

Serial electrocardiographic changes in a 14 year old Negro male who had been rendered temporarily unconscious by a stroke of lightning are presented. Deep symmetrical T wave inversion in Leads II III aVF V_1 V_2 with prolongation of the Q-T interval were interpreted as being compatible with diffuse myocardial injury. These changes resolved in approximately 12 months and no immediate or long term adverse effect upon the heart was clinically evident.

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Aneurysm of ventricular septum with outflow obstruction of the venous ventricle in corrected transposition of great vessels

Charles P. Summerall III MD*

George H. A. Clowds Jr MD*

John A. Boone MD***

Charleston SC

Complex or uncommon congenital malformations of the heart remain a challenge in diagnosis and in corrective surgery. Only recently have there been reports of the recognition and successful correction of outflow obstruction in the right ventricle due to an aneurysm of the membranous portion of the ventricular septum.^{1,2} The following case represents an unusual association of this lesion with corrected transposition of the great vessels and subaortic pulmonic stenosis.

Case report

A 2-year-old white boy (MCII 5250²) entered the Medical College Hospital on Jan 70 1968 for cardiac surgery.

In 1950 at the age of 8 1/2 yrs the patient had undergone cardiac evaluation because of a heart murmur first diagnosed prior to tonsillectomy when she was 4 1/2 years old. Her birth and infancy had been unremarkable. Her growth had been normal and she had had no similar symptoms. One of her three sisters had a small defect of the ventricular septum confirmed by cardiac catheterization. On physical examination the blood pressure was 110/70 mm Hg. There was no cyanosis. The second heart sound was loud in the pulmonic area. There was a thrill at the mitral and the left sternal border

most intense in the third intercostal space with an overlying thrill. An electrocardiogram showed hypertrophy of the right ventricle (Fig 1). Cardiac fluoroscopy suggested a ventricular septal defect. Catheterization of the right side of the heart revealed an increase in oxygen saturation from a level of 69 per cent low in the right atricle to 88 per cent in the outflow tract. The pressure in the right ventricle was 100/70 mm Hg. The tip of the catheter apparently passed through a ventricular septal defect into the aorta where the oxygen saturation was 92 per cent and the pressure 100/70 mm Hg. The pulmonary artery could not be entered.

Subsequently the patient lived an entirely normal life with no symptoms other than mild fatigability. In 1967 at the age of 20 years she had a nonventricular pregnancy. In 1964 in part because of increasing fatigability and occasional brief episodes of weakness she again underwent cardiac evaluation. Physical examination revealed a systolic murmur along the left sternal border with relative prominence of the second heart sound in the pulmonic area. An electrocardiogram showed hypertrophy of the right ventricle that was somewhat more marked than on previous tracings (Fig 1). Cardiac fluoroscopy with a normal lumbar. Cardiac catheterization revealed a pressure of 100/70 mm Hg in the right ventricle with no evidence from oxygen saturation data of a left to right shunt in the chamber. The pulmonary artery could not be entered. The thorax showed a small ventricular septal defect entered the left ventricle where the pressure was 90/70 mm Hg.

*Staff Department of Medicine, 4th Army Medical Center, Hospital Medical College of South Carolina, Charleston, SC.

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Address: Medicine, Department of Medicine, Medical College of South Carolina, Charleston, SC.

***Professor of Radiology, 4th Army Medical Center, Charleston, SC.

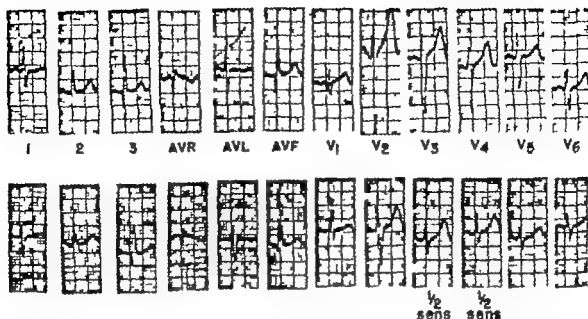


Fig 1 Standard electrocardiogram showing hypertrophy of the right ventricle when the patient was 8 years old (tracings at top) recorded on Oct. 3, 1950) and more advanced hypertrophy when she was 22 years old (tracings at bottom recorded on Dec. 8, 1963).

and the oxygen saturation was 95 per cent left ventriculography (Fig 2) demonstrated a prominent wedge in the upper portion of the septum in close relation to the aorta and the right coronary artery (Fig 3) showed a large filling defect in the outflow tract close to the pulmonary valve which was unusually low in position. The ventral contour of the ventricle was normal.

On Jan. 21, 1965 the patient underwent aortic exploration via median sternotomy with the use of cardiopulmonary bypass. The aorta and pulmonary artery were transected. Right atriotomy disclosed a small atrial septal defect. The atrioventricular valve appeared to be normal. A pulmonary arteriotomy permitted exploration of the right ventricle which contained a large aneurysm of the ventricular septum. During incision the aneurysm protruded into the outflow tract. It apparently produced a complete obstruction until the pressure in the right ventricle reached systemic level and partially emptied the aneurysmal sac to open a route for flow into the pulmonary artery. The aneurysm arose from a fibrous ring about 1 cm in diameter. There was no actual communication between the ventricles. The edges of the ring were closed with interrupted mattress sutures with inversion of the aneurysm sac into the left ventricle without perforating it. There was also a subchordal tendon curved by a thickened band of fibrous tissue which was partially excised. After thoracotomy prior to the repair the pressure in the right ventricle was 85/0 mm Hg and the pressure in the pulmonary artery was 25/5 mm Hg. After the repair the corresponding pressures were 33/0 and 10/0 mm Hg. The patient had an uncomplicated convalescence and returned to full

activity with relief of the previous symptoms. A moderately loud systolic murmur persisted. On May 15, 1965 the patient underwent right heart catheterization. The pressure in the right ventricle was 62/0 mm Hg and the systolic arterial pressure 90/70 mm Hg. Cineangiography demonstrated a residual subchordal pulmonary stenosis. No trace remained of the aneurysm of the ventricular septum.

Discussion

Aneurysms of the membranous portion of the ventricular septum constitute an unusual group of lesions that seldom have permitted accurate diagnosis during life. In an analysis of the anatomic and roentgenographic features of these defects Biron and associates¹ described several cases diagnosed by left ventriculography and they emphasized that wide prevalence of this technique would undoubtedly identify similar lesions with increasing frequency in a variety of clinical circumstances. Steinberg² reported the angiographic demonstration of a septal aneurysm in a 60 year old woman whom he studied in 1950 in all probability the earliest such diagnosis in a living patient. Two additional cases reported by Lekach³ and by Campbell and co-workers⁴ were

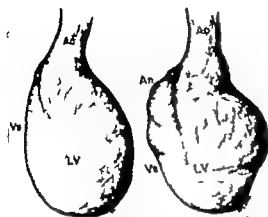


Fig. 2 Artistic drawing of cine left ventriculograms in diastole (left) and in systole (right). During systole the aneurysm (An) forms a prominent bulge in the upper portion of the ventricular septum (Vs) 13 mm medially inferior to the aortic root (Ao).



Fig. 3 Select right cine angiogram obtained in 1964 in the right anterior oblique projection. A prominent filling defect present in the ventricular outflow tract. The ventricular contour is triangular.

diagnosed by angiocardiology in essentially asymptomatic young women with loud systolic murmurs. In neither case was an intracardiac shunt detected. Schumaker and Clover⁷ studied a 6-year-old patient with the clinical and catheterization find-

ings of a small ventricular septal defect. Left ventriculography revealed a septal aneurysm which they corrected surgically. It arose from a base 12 mm in diameter and contained a 3 mm interventricular communication. Perazulo and associates⁸ reported their findings in a 27-year-old woman in whom the catheterization data indicated a large left-to-right shunt at the ventricular level and a systolic pressure gradient of 50 mm Hg in the right ventricular outflow tract. At operation they found an aneurysm 4 cm in length and 3 cm in diameter which protruded into the right ventricle below the crista supraventricularis and partially obstructed the infundibulum. This aneurysm contained a 1 cm interventricular communication. Das Jhinka and Walker⁹ reported a similar lesion in a 12-year-old girl in whom the catheterization data had shown a moderate left-to-right shunt at the ventricular level and a systolic gradient of 20 mm Hg in the outflow tract.

Our patient presented two unusual and closely related features. She had corrected transposition of the great vessels and a marked degree of obstruction of the outflow tract of the venous ventricle with a systolic gradient of 50 mm Hg measured at operation. Angiocardiographic studies had suggested the positional transposition of the aorta and the pulmonary artery as confirmed at surgery and there was obvious functional correction. Other roentgenographic features conformed to the criteria suggested by Ellis and co-workers¹ for the diagnosis of corrected transposition: (1) proximity of the pulmonary valve to the right atrioventricular valve without interposition of a crista supraventricularis or infundibulum and (2) smooth internal contour of the venous ventricle. At operation the base of the aneurysm of the membranous septum was close to the pulmonary valve which permitted exposure and repair through a pulmonary arteryotomy. Examination of the right atrioventricular valve at operation revealed no distinct abnormality although postoperative angiocardigrams suggested that this valve was in fact bicuspid and structurally similar to a normal mitral valve.

The anatomic relationships of the membranous portion of the ventricular septum

in corrected transposition of the great vessels clearly predisposed to the high degree of obstruction of the outflow tract that was observed in this patient. In a normal heart the membranous septum lies close to the aortic valve with its inter-ventricular component placed immediately below the right coronary aortic cusp. In the right ventricle the membranous portion of the septum lies below the crista supraventricularis and an aneurysm projecting at this site into the lumen of the ventricle will not cause serious obstruction unless it reaches considerable size. With inversion of the ventricles however these relationships are reversed. The crista supraventricularis lies in the arterial ventricle. The outflow tract of the venous ventricle is short and an aneurysm arising in the membranous septum will project into the outflow tract immediately below the pulmonary valve. Some degree of obstruction of the outflow tract is inevitable.

The specific pathogenesis of aneurysms of the membranous portion of the ventricular septum is controversial. Lev and Saphir⁸ in an extensive review of this anomaly agreed with a theory proposed by Mall in 1912 who postulated that the membranous septum lying somewhat tangential to the root of the aorta could be structurally weakened by a minor degree of rightward displacement of the bulbar septum. After birth high pressures in the left ventricle would then progressively distend the aneurysmal sac. In support of a close relationship between abnormalities of the aortic root and aneurysms of the membranous septum these authors cited from the literature 3 cases of aneurysms in both the membranous septum and in the sinus of Valsalva and 6 cases of aneurysms involving the aorta and the membranous septum in continuity. They discussed however the alternative possibilities that aneurysms of the membranous septum might result from (1) defective formation of the endocardial cushions or (2) isolated defective fusion of the proximal bulbar swellings. Baron and associates² in evaluating Mall's theory could find no evidence of an abnormality of the aortic root in their clinical series or in 2 autopsy cases of septal aneurysms. The occurrence of such aneurysms in patients with corrected transposi-

tion of the great vessels as in this case and in an autopsy case mentioned by Baron² is also somewhat at variance with Mall's theory for with ventricular inversion the membranous septum loses its close relationship to the aortic root. These considerations tend to implicate a defect in the complex fusion of the muscular septum, the endocardial cushions and the conus ridges rather than a displacement of the bulbar septum as the principal feature in the pathogenesis of congenital septal aneurysms.

An additional feature of this case was the presence of subvalvular pulmonic stenosis. The obstruction may well have resulted from a flap of accessory valve tissue arising from the pulmonary and aortic ventricular valves comparable to the lesions described by Levy and co-authors¹¹ in 3 cases of corrected transposition of the great vessels. Such a lesion would explain the difficulty encountered during heart catheterization in advancing the tip of the catheter into the pulmonary artery. Isolated subvalvular stenosis was not encountered in 33 cases of corrected transposition of the great vessels reviewed by Schiebler and associates¹² although pulmonic valvular or combined valvular and subvalvular stenosis was present in 6 of these cases.

A further aspect of this case is the apparent late spontaneous closure of a defect of the ventricular septum initially demonstrated by heart catheterization when the patient was 8 years old. Although the significance at that time of the oxygen saturation data which suggested a bidirectional shunt at the ventricular level is open to question the pressure data clearly demonstrated that the catheter passed through the ventricular septum into the aorta. Fourteen years later there was no evidence of such a defect by angiocardiorraphy or at surgical exploration.

Summary

This report describes a patient with corrected transposition of the great vessels and with an aneurysm of the membranous portion of the ventricular septum which was surgically repaired. The aneurysm caused obstruction of the outflow tract of the venous ventricle a hemodynamic com-

plication that is essentially inevitable when an aneurysm of significant size develops in the presence of ventricular inversion. Subvalvular pulmonary stenosis was also present.

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Clinical pathologic conference

James H. Muller, M.D.

George R. Noren, M.D.

Paul R. David, M.D.

Kurt Amplatz, M.D.

Vladimir I. Kanjuh, M.D.

Jesse E. Edwards, M.D.*

Minneapolis and St. Paul, Minn.

DR. MULLER: This 6-month-old infant was the product of the third pregnancy of a 29-year-old mother. The child was delivered after 38 weeks of gestation and the birth weight was 4 pounds and 13 ounces. The infant did not cry at birth and during his first 24 hours of life the mother was told that the child had congenital cardiac disease. The infant gained weight during the first 6 months of life and was generally asymptomatic until 3 days prior to admission, when he became anorectic and pale and experienced difficulty in breathing. On admission to the University of Minnesota Hospitals he presented as a pale, irritable infant. The pulse rate was 160 per minute and the respiratory rate was 48 per minute. The lungs were clear. No murmur was present but the pulmonary component of the second cardiac sound was accentuated. The hemoglobin concentration in the blood and the leukocyte blood count were normal.

The electrocardiogram (Fig. 1) revealed signs of right atrial enlargement and of marked right ventricular hypertrophy. The thoracic roentgenogram showed enlargement of the right side of the heart with a normal-sized left atrium (Fig. 2).

The pulmonary fields showed a pattern of pulmonary venous obstruction. The infant was digitalized and placed in a croup tent.

During the period of hospitalization the infant manifested recurrent episodes of acute pulmonary edema, each characterized by marked dyspnea, pallor, and the presence of pulmonary râles. These attacks were treated with morphine sulfate and phlebotomy, and during one such episode 2 weeks after admission the infant died.

During the infant's life a venous angiogram had been recorded. This demonstrated no right to left shunt at either the atrial or ventricular levels. The circulation through the pulmonary circuit was very slow, and the pulmonary veins were not delineated, although a small amount of contrast material was seen to enter the left atrium. Dr. Noren will describe the catheterization findings.

DR. NOREN: Cardiac catheterization was performed twice (Table 1). These studies demonstrated pulmonary arterial hypertension with an elevated pulmonary arterial wedge pressure. Three pulmonary veins were catheterized from the left atrium, and in each the pulmonary venous

* In the Department of Pediatrics, University of Minnesota, St. Paul, Minn. (Dr. Muller).
Department of Pathology, University of Minnesota, St. Paul, Minn. (Dr. David).
Department of Pathology, University of Minnesota, St. Paul, Minn. (Dr. Noren).
Department of Pathology, University of Minnesota, St. Paul, Minn. (Dr. Amplatz).
Department of Pathology, University of Minnesota, St. Paul, Minn. (Dr. Kanjuh).
Received for publication, September 1, 1964.
Address: Department of Pathology, University of Minnesota, St. Paul, Minn. 55102.

Table I Synopsis of data obtained at each cardiac catheterization

Site	First catheterization		Second catheterization
	Oxygen saturation (per cent)	Pressure (mm Hg)	Pressure (mm Hg)
Superior vena cava	30	—	—
Inferior vena cava	30	—	—
Right atrium	30	8/2.2	12/7.8
Right ventricle	30	75/0 12	100/0
Pulmonary artery	30	75/30 50	100/40 50
Pulmonary arterial wedge	—	37/13 70	37/15 30
Pulmonary edema	85	27/17 23	—
Left atrium	85	22/10	17/5 12 5

pressure was higher than the left atrial pressure

At the time of the first catheterization a selective pulmonary arteriogram was recorded which revealed slow circulation through the pulmonary circuit. The pulmonary veins were not clearly delineated. The left atrium was demonstrated to be of normal size. At the time of the second cardiac catheterization a left atrium was obtained. This demonstrated that the left atrium and left ventricle were each of normal size. There was no reflux of contrast material into the pulmonary veins.

DR WOLFE: Dr David, would you discuss the differential diagnosis?

DR DAVID: This 6-month-old infant exhibited manifestations of cardiopulmonary disease. Initially, when a physician sees an infant with tachypnea and tachycardia but without a cardiac murmur, he strongly considers pulmonary disease.

The increased anteroposterior diameter of the thoracic cage, electrocardiographic signs of marked right ventricular hypertrophy, and the auscultatory findings of pulmonary hypertension exhibited by this infant could be manifestations either of

severe chronic acquired or congenital pulmonary disease or of a cardiovascular malformation. The degree of right ventricular hypertrophy indicated by the electrocardiogram would appear to be unusual for chronic pulmonary disease at this age, particularly in view of the lack of pulmonary symptoms during the major portion of the infant's life.

The thoracic roentgenograms may give us an impression of whether pulmonary disease is present. May we see these, please, Dr Amplatz?

DR AMPLATZ: In this age group it is of course very difficult to differentiate between increased pulmonary vascularity and pulmonary disease. As may be seen, however (Fig. 2), the pulmonary densities are so diffuse and the heart so definitely enlarged that we would very strongly consider pulmonary edema rather than parenchymal disease of the lungs. If pulmonary disease is present, it may be in the form of pulmonary hemosiderosis secondary to venous obstruction. The roentgenogram in fact is demonstrative of the latter condition.

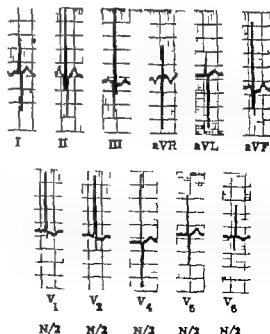


Fig. 1. The electrocardiogram.



Fig. 2. Anteroposterior thoracic roentgenogram. Moderate cardiomegaly; pre-aortic diffuse granular appearance; evidence of the pulmonary venous field.

DR. DAVID: We agree with the interpretation of Dr. Amplatz that there is no evidence of pulmonary parenchymal disease and we will focus attention on the cardiovascular system. The elevated pulmonary arterial wedge pressure confirms the presence of a cardiac lesion on the left side. The diffuse venous congestion or so called ground glass appearance of the pulmonary fields demonstrated in the thoracic roentgenogram is suggestive of pulmonary venous obstruction. These features represent the foundation upon which to build a differential diagnosis.

Several cardiovascular malformations are associated with the roentgenographic picture of pulmonary venous obstruction. Lucas and associates¹ reviewed the problem of pulmonary venous obstruction in the pediatric age group and on the basis of the electrocardiogram divided cases of pulmonary venous obstruction into two groups: (1) those with signs of right ventricular hypertrophy and (2) those with signs of biventricular hypertrophy. The former group was considered to be indicative of obstruction to pulmonary venous return located at or proximal to the mitral valve whereas in the latter group the lesion is located distal to the mitral valve as in aortic stenosis, coarctation of the aorta and other lesions causing left ventricular hypertrophy.

This broad approach is applicable in

our case. One must recognize however that certain conditions distal to the mitral valve may give electrocardiographic signs of only right ventricular hypertrophy. Such conditions include endocardial fibroelastosis with hypoplasia of the left ventricle and hypoplastic left ventricle with atresia or stenosis of the aortic valve. Each of these conditions was excluded by the angiographic findings of a normal sized left ventricle. On the basis of the roentgenographic and electrocardiographic evidence of right ventricular hypertrophy we know that the obstructive anomaly is at or proximal to the level of the mitral valve and several diagnostic possibilities exist.

One of these is total anomalous pulmonary venous connection with obstruction to the pulmonary venous return but several features exclude this condition. The catheterization data and angiographic features indicate no hemodynamically significant atrial defects. A pressure difference of 14 mm Hg exists between the right atrium and the left atrium which is important evidence against the presence of an atrial septal defect. No arterIALIZATION was present in the chambers on the right side or in the venous vessels. A venous angiogram failed to demonstrate a right to left shunt.

Congenital mitral stenosis should be considered in the differential diagnosis but this malformation is usually accompanied by a cardiac murmur. The absence of radiologic and electrocardiographic evidence of left atrial enlargement does not eliminate this possibility since the left atrium is not necessarily enlarged in this condition in infancy. The normal left atrial pressure in the presence of an intact atrial septum eliminates consideration of any other significant obstructive lesions such as supraventricular stenosing ring at the level of the mitral valve.

The reported left atrial pressures are confusing. The pressure recorded during the first catheterization was elevated but during the second cardiac catheterization the values were considered to be normal. I think that in such cases the wave form or shape of the pressure curve may be decisive in the interpretation. Normally the *a* wave is predominant



Fig. 3 Left atrial angiogram. *a*, Anteroposterior projection. *b*, Lateral projection. Densely opacified left atrium without reflux of contrast material into pulmonary veins. Left ventricle and aorta are of normal size.

in the left atrium. A predominant *a* wave which was present in this case would favor either mitral stenosis or lack of compliance of the left ventricle (in this case a hypoplastic left ventricle). Dr. Noren: Was there anything significant about the left atrial pulse pressure curve?

DR. NORRIS: The left atrial pressure revealed an elevated *a* wave as recorded with the tip of the catheter positioned in the left atrial appendage. It is known that pressures recorded at this site will exhibit falsely elevated *a* waves. The left atrial pressures obtained during the second catheterization were measured at a site above the mitral valve.

DR. DAVID: Now may we see the left atrial angiogram?

DR. AMPLATZ: The left angiogram shows a normal sized very densely opacified chamber (Fig. 3). Emptying is perhaps slightly slower than normal and in keeping with a small cardiac output. The mitral valvular area is not remarkable angiographically. There is no regurgitation of contrast material into the pulmonary veins a phenomenon which is commonly seen in left atriongrams. The left atrium is well opacified; the significance of this finding however is not certain.

DR. DAVID: The left atrium shows no

hold up of contrast material and this finding is further evidence against either mitral stenosis or stenosing supraventricular ring. The data from each catheterization study indicate a pressure gradient between the level of the pulmonary capillaries and the left atrium. The gradient was 10 mm Hg at the time of the first catheterization and 20 mm during the second study. This evidence suggests that the obstructive lesion lies between the pulmonary capillary bed and the left atrium.

Three types of obstructive lesions may be encountered at the junction of the pulmonary veins with the left atrium. These are cor triatriatum, stenosis of individual pulmonary veins and hypoplasia of the common pulmonary vein.

In adults cor triatriatum is commonly accompanied by a cardiac murmur whereas in only 50 per cent of children and infants is one present. The angiographic studies have demonstrated a normal size and a normal shape of the left atrium which is contrary to the case in cor triatriatum. The classic angiographic picture is one of a reduced distal atrial chamber with a flat or cut-off superior partition.

In addition in our patient the tip of the catheter was directed into three of the pulmonary veins from the left atrium, a

phenomenon that would be unusual in the classic case of cor triatriatum. It is possible however that the pulmonary veins were catheterized through a hypoplastic common pulmonary vein. For this reason the fact that the pressure was higher in the pulmonary veins than in the left atrium does not aid in differentiating between the cor triatriatum and stenosis of individual pulmonary veins. In addition the elevation of pulmonary venous pressure may be a reflection of the pulmonary arterial pressure and in my opinion this finding is of no diagnostic value. The pulmonary angiogram may be most useful in delineating the pulmonary venous system. Dr Amplat did the pulmonary arteriogram in this case delineate the pulmonary venous system.

DR AMPLATZ: In this case the delineation of pulmonary veins was so poor that anatomic information was not obtained. On the other hand the fact that the left atrium opacified even faintly was most useful in excluding the possibility of total anomalous pulmonary venous drainage with obstruction.

DR DAVID: With the angiographic findings I would favor the diagnosis of stenosis of the individual pulmonary veins for three reasons. First there was lack of visualization of a third atrial chamber as would be apparent in cor triatriatum. Second the poor delineation of the pulmonary veins would be expected in stenosis of the individual pulmonary veins. Third the fact that the tip of the catheter could be directed into three of the pulmonary veins would be most unusual in a case of classic cor triatriatum. Therefore my diagnosis is stenosis of the individual pulmonary veins.

DR MOLLER: Dr Kanjuh will present the necropsy findings.

DR KANJUH: Each of the pulmonary veins joined the left atrium at normal sites (Fig 4). The left lower right upper and right lower pulmonary veins were hypoplastic over the major portions of their respective courses yielding an orifice of only about 1 mm in diameter for each vein. The left upper pulmonary vein appeared to be normal having an orifice of 3 mm in diameter. Although no localized gross constrictive lesions were identified



Fig. 4 The left side of the heart and the pulmonary veins. The lung have been turned so that the apex of the upper lobes appear at the lower portion of the illustration. The right upper and lower pulmonary veins (RL and RU) and the left lower (LL) pulmonary vein are hypoplastic. The left upper pulmonary vein (LU) is of normal size. The left atrium and the mitral valve are not remarkable.

in the pulmonary veins each of the hypoplastic veins showed focal intimal thickening mainly with fibrous tissue but also with smooth muscle in some areas (Fig 5). The basic structure of the heart was normal but right ventricular hypertrophy was a marked feature (Fig 6). The foramen ovale showed characteristics of valvular competent patency. No ventricular septal defect was present. The ductus arteriosus was closed. An anomalous origin of the right subclavian artery from the aorta was identified. The exterior of the lungs was characterized by evidence of prominent visceral pleural lymphatics and there was marked edema. The basic color of the pulmonary tissue was tan suggesting hemorrhage. The histologic appearance of the lungs was characterized by prominence and engorgement of the alveolar capillaries. Medial hypertrophy of the small muscular arteries was prominent and muscularization of arterioles was a striking feature. Pleural and parenchymal lymphatics were wide. The pulmonary veins



Fig 3 Photomicrographs of pulmonary veins. Left lower pulmonary vein shows focal intimal thickening. Elastic tissue stain $\times 40$. b Left upper pulmonary vein structure is normal. Elastic tissue stain $\times 10$. c Right lower pulmonary vein shows focal intimal thickening. Elastic tissue stain $\times 40$. d Right upper pulmonary vein pad of fibrous intimal thickening. Elastic tissue stain $\times 110$.



Fig 6 Right atricle Prominent right atricular pericardium. The atricular septum is intact.

showed varying degrees of medial hypertrophy. No distinctive differences could be identified in histologic structure between those lobes in which the pulmonary veins were hypoplastic and the upper lobe of the left lung in which the pulmonary vein was normal.

DR MOLLER: Dr Edwards, would you please give a closing summary?

DR EDWARDS: The pathologic findings of severe degrees of pulmonary stenosis involving three of the four pulmonary veins is in keeping with the clinical features.

Stenotic lesions of the pulmonary veins may be divided into two major groups as follows: (a) those occurring in pulmonary veins that join the left atrium and (b) those in channels which are anomalously terminating veins.² Stenosis of anomalously-terminating pulmonary veins may result from (a) hypoplasia of such veins,² (b) focal fibrous lesions of the intima,⁴ and (c) compression of veins by contiguous structures. One example of the latter process occurs in that condition in which there is total anomalous pulmonary venous connection to a vein of the portal system. Such veins pass through the esophageal hiatus of the diaphragm in company with the esophagus. Obstruction to the pulmonary venous system may occur when food passes down the esophagus.¹

A second situation in which an anomalous pulmonary vein is obstructed occurs in those instances of total anomalous pul-

monary venous connection to the left innominate veins in which the anomalous vein ascends between the left pulmonary artery and left main bronchus.^{3,5}

Let us return to the condition represented by the case herein presented, that in which stenotic lesions occur in pulmonary veins which connect with the left atrium—a condition which has been termed stenosis of individual pulmonary veins. This condition may involve only one, several or each of the pulmonary veins. The lesions may appear either alone or in association with a variety of cardiac malformations.

Among the relatively small number of reported cases of stenosis of each of the pulmonary veins, an atrial septal defect has been associated in a few.^{7,8} The case presented in this conference is rare in that no cardiac malformation was associated with the pulmonary venous lesions. The stenotic lesions usually are rather sharply localized to the veno-left atrial junction, the stenosis being caused by intimal fibrous hyperplasia. In such cases there is a potential for surgical correction. A contrasting situation is presented by this case in that in addition to intimal lesions, the disease in the pulmonary veins was characterized by long segments of hypoplasia.

Of interest in the case presented is the fact that no histologic differences could be identified between the pulmonary lobe from which the veins were obstructed and the lobe without stenosis of its vein. The probable explanation for this is that most of the blood circulating through the lungs must have passed through the upper lobe of the left lung. The volume of blood passing through the anatomically left upper pulmonary vein must have exceeded its anticipated capacity, so that this vein was functionally stenotic to the volume of blood entering it.

Diagnosis: Congenital stenosis of individual pulmonary veins without intra-cardiac anomalies.

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Fundamentals of clinical cardiology

Emotional and sensory stress factors in myocardial pathology

Neurogenic and hormonal mechanisms in
pathogenesis, therapy and prevention

W. Raab MD FACC*
Burlington Vt

The approach to the controversial problem of emotional factors in the pathogenesis and preventability of degenerative heart disease is handicapped by several interacting difficulties: the complexity of mechanisms involved, semantic ambiguities and the lack of coordination of masses of largely unutilized information incoherently scattered throughout the world literature.

In the following an attempt will be made to cope in this particular field with the growing demand for general broader knowledge integration through comprehensive reviews of the literature.^{1,2}

In recent years several conferences were devoted to certain aspects of psychogenic cardiovascular regulation and pathology.³⁻⁶ However none of them concentrated on the emotion related physiological and biochemical phenomena under discussion with regard to their direct interference in the metabolism and structure of the heart muscle. Yet these very interferences are of primary significance for the problem of degenerative heart disease. This was explicitly acknowledged by the Second National Conference on

Cardiovascular Diseases in Washington in 1964. Its official summary emphasizes that the pathogenic role of psychological and higher nervous functions has received far less attention than their importance deserves and that studies in this direction should be given a new public face and unusually long term support.⁷

1. Scope of the problem complex

The heart muscle itself and those of its functional metabolic and structural qualities which are affected by influences from the central nervous system constitute the main object of numerous studies focused on the problem complex of degenerative (so called coronary or ischemic) heart disease. Autonomic nervous, neurohormonal and endocrine mechanisms represent under sensory and emotional stress conditions the mediators of pathogenic modifications of cardiac metabolism. Socioeconomic, environmental and other emotional factors provide an important part of the ultimate background for cardiac degenerative changes and death.

It should be pointed out however that

* is the Department of Medicine, Cardiac Research Unit, DeGaulle and Memorial Hospitals and University of Vermont College of Medicine, Burlington, Vt.

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Address: University of Vermont College of Medicine, Burlington, Vt 05401

at least in the human being emotional and sensory stress mechanisms as such are only infrequently sufficiently cardiotoxic to produce serious lesions in an otherwise normal heart muscle whose vulnerability is not simultaneously augmented by other co-existing derangements pertaining to the wide spectrum of jointly contributing pathogenic factors.

In order to understand the origin of hypoxic heart disease it is necessary to keep in mind the fundamental fact that contrary to traditional beliefs injurious myocardial hypoxia does not always result merely from a sclerotic narrowing of the coronary arterial branches^{10,11} (except for extreme stenosis or occlusion). The occurrence of hypoxia in certain areas of the myocardial tissue depends rather on the coincidence of a locally reduced vascular oxygen supply (e.g. due to coronary atherosclerosis) and an absolute or relative exaggeration of myocardial oxygen consumption in other words on a local discrepancy between oxygen availability and demand. The latter is specifically augmented by the catecholamine liberating and thus oxygen wasting activity of the cardiac sympathetic nerves.

An acute or sustained sympathetic adrenergic overactivity is elicited by emotional and sensory stresses which are associated with central nervous stimulation of the sympathetic and the sympathetic controlled adrenomedullary system¹². Aside from their catecholamine mediated interference in myocardial oxygen economy central nervous stimuli are also responsible for stress-induced discharges of adrenal corticoids which together with catecholamine action affect myocardial electrolyte balance and for the mobilization of free fatty acids from adipose tissue as well as of other lipids possible from the liver.

Thus we will have to proceed step by step tracing the various neurogenic hormonal and cardiometabolic mechanisms which according to present-day knowledge contribute jointly to the mass mortality from degenerative heart disease in highly civilized prosperous nations notably in the U.S.A.

Particular attention will hereby be paid to the behavior of catecholamines and adrenal corticoids in view of the well

known potential cardiotoxicity of the former¹³ and its marked exaggeration by the latter¹⁴.

II Emotional and sensory stress induced liberation of catecholamines

Harpalus and Kresell's¹⁵ discovery of functional connections between the central nervous and the peripheral sympathetic systems and Cannon's¹⁷ classic studies concerning the activation of the latter under the influence of emotional and sensory stimuli laid the foundations for today's concepts of psychosomatic interrelationships in cardiovascular physiology and pathophysiology.

Both the cerebral cortex the hypothalamus and the reticular substance^{18,19} participate in the activation of catecholamine liberating sympathetic pathways within the framework of mental processes. Whether reciprocal feedback mechanisms (e.g. retrograde stimulation of central structures by peripherally discharged epinephrine^{20,21}) are hereby involved remains a matter of conjecture.

Significant and sometimes very marked augmentations of urinary catecholamine excretion have been observed with great regularity under various kinds of emotional and sensory stresses and tensions such as scholastic examinations^{22,23} admission to a hospital²⁴ airplane flying²⁵ viewing exciting films²⁶ performing exacting industrial or office work with annoying noise and light disturbances²⁷ etc. Even the anticipation of an uncomfortable experience²⁸ can be associated with an elevation of the urinary catecholamine level.

In general it can be said that all anxiety provoking situations are characterized by a high excretion of epinephrine with only slight or no increase in norepinephrine²⁹ whereas under attitudes of aggressiveness the excretion of norepinephrine comes more to the foreground^{30,31}. Augmentations of urinary catecholamines were also observed under conditions of pleasurable excitement³² and sexual arousal³³. By contrast the viewing of peaceful serene nature films was accompanied by a drop in the catecholamine excretion below the control level.

Diurnal fluctuations chiefly of epinephrine

rine are of considerable magnitude with peaks in the afternoon and low points after midnight.²²

The catecholamine metabolite vanillin mandelic acid (VMA) was likewise found to be augmented in the urine in states of anxiety, tension,¹ and anticipation^{23,24} e.g. while driving a car²⁵ etc.

During states of mania in psychotic patients the excretion of epinephrine was found to be increased with little or no change in norepinephrine.^{26,27} Mental depressions do not seem to exert a characteristic influence on the production of catecholamines.^{28,29,30}

Temperamental differences between high strung ambitious personality types and their placid easy going counterparts appear to be reflected in a higher urinary norepinephrine excretion in the former.³¹ Low levels of catecholamine excretion were observed in emotionally stable primitive African nomadic natives.³²

In monkeys plasma levels of norepinephrine rose during various experimentally induced emotional disturbances. Increases in epinephrine were most closely connected with situations of uncertainty and threat.³³ Similar reactions of the plasma catecholamines occur in man under intensive emotional stress.⁴ During 6 minutes of a milder mental stress (arithmetical) no significant changes in the plasma norepinephrine concentration were observed.³⁴

In summary an augmented liberation of adrenosympathetic catecholamines appears to be well established as a typical sequel of emotional and sensory central nervous stimulation. Epinephrine discharges seem to be prevalent mainly in situations of passive anxiety whereas norepinephrine is mobilized during attitudes of aggressiveness and violent action.

III Influence of central nervous, emotional, and sensory stimuli upon cardiac rhythm, dynamics, and ECG

Cardiac acceleration occurs under a great variety of emotionally significant circumstances as a catecholamine mediated result of centrally elicited sympathetic nerve stimulation.^{4,35,36}

Sudden fright may be associated with a short lasting vagotonic bradycardia or even cardiac standstill.^{4,37,38} Anxiety⁴⁰ and

HEART RATE ISOMETRIC PERIOD

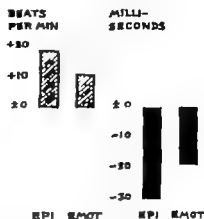


Fig. 1 Adrenergic effects of infused epinephrine (0.1 mg/kg min) and of emotion induced catecholamine action (students immediately before examination) on heart rate and isometric tension period of left ventricle. Shortening of the latter is a sensitive criterion of adrenergic increase in myocardial oxygen consumption. (For detail see Raab et al. *Cardiologia* 33:350 1958.)

anticipatory tension on the other hand evoke moderate to marked accelerations of the heartbeat. This is the case for example before imminent scholastic examinations and contests^{41,42} (Fig. 1) during exciting discussions^{43,44} in response to verbal stimuli⁴⁵ during arousal of feelings of hostility⁴⁶ watching sports games⁴⁷ etc. Likewise intellectual effort under pressure as in performing supervised mental arithmetic^{48,49} and sensory annoyances such as noise^{50,51,52} or flickering light^{53,54} induce various degrees of tachycardia.

The cardiac output is augmented under the aforementioned emotional and sensory stimulations.^{55,56,57,58} The usual exercise induced cardiac acceleration was found to be further exaggerated during emotional stress⁵⁹ or acoustical annoyances⁶⁰ and the postexercise deceleration was retarded.⁶¹

An increase in the heart rate can be elicited by symbolic stimuli e.g. by the mere discussion of exercising⁶² and conditioned reflex mechanisms are apt to maintain acquired cardiac chronotropic reactions to conditioning stimuli over long periods of time.⁶³

Shortening of the isometric tension period of the left ventricle is a sensitive criterion of adrenergic inotropic action.

NEUROGENIC CARDIAC RISK FACTOR SCREENING TEST

RESTING VALUES (200 SUBJECTS)

HEART RATE	per min	46-100 (ave 61)
ISOMETRIC PERIOD (mm Hg)		61-135 (ave 93)
SYSTOLIC BL PR (mm Hg)		90-170 (ave 115)
DIASTOLIC BL PR (mm Hg)		50-110 (ave 75)

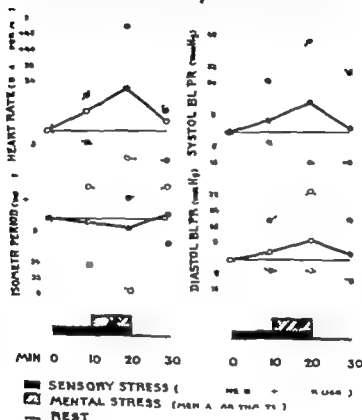


Fig. 2 Ranges (dashed lines) and averages (solid lines) of deviations from resting heart rate, isometric tension, period, systolic and diastolic blood pressure in response to standard sensory plus mental stresses (20 minutes of rhythmic telephone bell ringing and flickering light, 10 minutes of mental arithmetic) followed by a 10 minute recovery period. (From Raab and Kuzynski, *American Journal of Cardiology* 16:42, 1965, by permission.)

Accordingly, it occurs during both sensory⁴ (noise, flickering light) and mental stresses^{11,12} (Figs. 1 and 2).

Emotion-induced cardiac acceleration and corresponding changes in the electroencephalogram make their appearance simultaneously.¹⁰

In two small groups, one of high strung and the other of placid individuals, no significant difference was found in total 48-hour average heart rates.¹³ On the other hand, in a larger series, the resting heart rate of emotionally irritable tense

persons proved to be significantly higher than that of leisurely individuals who had a more neutral temperament.¹⁴ Cardiac responses (acceleration and shortening of the isometric tension period) occurred likewise on a higher level in the former group¹⁵ (Fig. 3) and the relative length of the left ventricular systole in per cent of the cardiac cycle was prolonged in the emotionally irritable subjects.¹⁶

Besides tachycardia^{17,18} and a combination of tachycardia with feelings of anxiety,¹⁹ experimental cortical and sub-



Fig. 3 Cardiac responses to the same test procedure as in Fig. 2, grouped according to personality patterns. 49 subjects with high 28 with low emotional excitability (according to self evaluation by prestressor and point scoring). The cardiac sympathetic resting tone and stress response is higher in the excitable subjects and lower in the stable ones. (From Raab and Kraybill, *American Journal of Cardiology*, 16:42, 1965, by permission.)

ortical stimulations can also elicit other abnormalities of the cardiac rhythm including vagal bradycardia depending on the location of the stimulated areas.

Ectopic beats^{73, 74, 75} and other arrhythmias^{73, 74} were thus artificially provoked and inversions of T as well as ST segment displacements appeared to be indicative of myocardial hypoxia^{73, 74}. It is worthy of note that under such experimental conditions the epinephrine content of the heart muscle was markedly augmented presumably because of neurogenic discharges from the adrenal medulla whose epinephrine stores were simultaneously found to be reduced.⁷⁶

Local stimulation of the stellate ganglia on the other hand was followed by accumulation of norepinephrine in the myo-

cardium.⁷⁷ Both catecholamines if present in excess are known to produce hypoxic changes in the electrocardiogram.

Alterations of the cardiac rhythm and the electrocardiogram similar to those experimentally induced by stimulation of the central nervous system are not so frequently observed as spontaneous events under emotional stresses. They include supraventricular and ventricular premature contractions, paroxysmal atrial nodal and ventricular tachycardia and presumably due to vagal participation paroxysmal atrial fibrillation and A-V block^{78, 79, 80} especially in the presence of arteriosclerotic vascular changes in the vicinity of the atrioatrial node and the A-V conduction system.⁸¹

Inadequate compensatory dilatability of the coronary arteries which supply the myocardium of the left ventricle facilitates the appearance of isoxic patterns in the electrocardiographic ventricular complex under emotionally provoked neurogenic catecholamine action. This occurs in a similar fashion when manifestations of ventricular anoxia are evoked by mere sympathetic stimulation when coronary dilatability is artificially impaired.^{82, 83}

Such electrocardiographic changes especially inversion of T and displacement of ST have been observed under a variety of acute or prolonged emotional stimuli and stresses such as verbal stimulation⁸⁴ watching sports games⁸⁵ violent arguments⁸⁶ admission to prison⁸⁶ listening to stirring music⁸⁷ impending surgery^{88, 89} and other states of anxiety and emotional excitement^{89, 90, 91} (Fig. 4) including anxiety neurosis⁹² and hypnotically suggested emotionally stressful situations.^{93, 94}

Inversions of T and elevations of the ST segment were also recorded in neurotic baboons^{95, 96} with intact coronary arteries.

Anxiety seems to be a particularly effective emotional element in eliciting myocardial ischemic changes but no clearly specific differentiations have been made between patterns provoked by anxiety and those provoked by other emotional stresses. They all point to catecholamine mediated neurogenic interferences in myocardial oxygen economy.

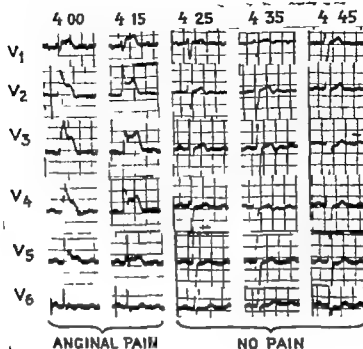


Fig. 4. Anatomic upward displacement of ST segment during emotion induced attack of angina pectoris subsiding within 25 minutes.

IV Emotion induced catecholamine mediated angina pectoris and sudden death

The nearly 30 year old long rejected or disregarded concept of a fundamental causal involvement of myocardial oxygen consumption-augmenting catecholamines in the clinical syndrome of angina pectoris is today so widely accepted and adopted⁹⁰⁻¹⁰⁰ that it does not require a detailed repetition here.

The only important amplification of its basic principle was contributed by von Euler's discovery in 1916 of norepinephrine as the intramyocardially liberated neurohormone of the sympathetic nervous system.¹⁰¹

The typical provocation of anginal symptoms by acute emotional arousal¹⁰² rather than by chronic emotional tensions¹⁰³ is one of the best known examples of psychosomatic pathology. Its causal connection with catecholamine liberation, emotional central nervous stimulations (see Section II) elevated catecholamine level in the blood plasma,⁹⁹ increased catecholamine metabolites in the urine¹⁰⁴

and the familiar catecholamine induced increase in myocardial oxygen consumption¹⁰⁷ appears to be well established.

Such emotional stimuli and catecholamine discharges from the adrenal medulla and from the cardiac sympathetic nerve terminals in order to elicit myocardial hypoxia in circumscribed areas of the myocardium¹⁰⁸ require in general the predisposing presence of atherosclerotic coronary narrowings. This constellation of circumstances could be experimentally duplicated by combining cardiac sympathetic stimulation or injection of catecholamines with an artificial limitation of coronary dilatability⁹⁷ (Fig. 5).

Significantly various antisympathetic measures such as the administration of tranquilizing drugs,^{99,111} thoracic sympathectomy,¹¹² epinephrine secretion reducing x-ray irradiation of the adrenal glands,¹¹³ emotion suppressing antithyroid treatment¹¹⁴ and ganglionic and beta receptor blockers have been found to be useful in the treatment of angina pectoris.

The usually short duration of anginal attacks even if the underlying emotional

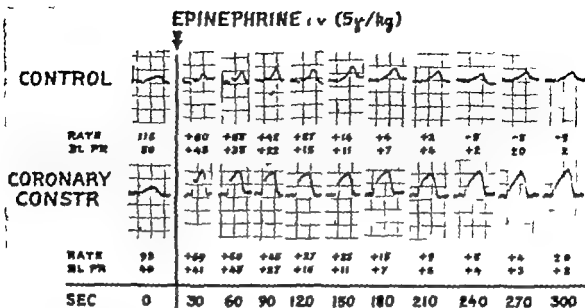


Fig. 5 Hyperventilating (5 l/min) effect of infused epinephrine on a patient presented by intermittent of chest pain, coronary dilatability through enough sitting but not a full sitting (from Raab et al. *American Journal of Cardiology* 9:3 1967) (reprinted with permission).

situation persists, suggests some self-regulatory mechanism such as possible vasodilating effect of accumulated lactic acid.¹¹

Sudden unexpected death has been observed with relative frequency in close time relationship and evident causal connection with acute emotional events e.g. an excited argument, stressful interview, the receipt of some crushing news or a sudden fright.^{11,12}

For obvious reasons the exact physiological and biochemical mechanisms involved at the crucial moment remain unknown as a rule but it can be assumed by inference that either ventricular fibrillation or cholinergic ventricular standstill have occurred,¹ the latter being more likely the result of fright than of anger or grief.

In more than 90 per cent of a series of instances of unexpected death occurring within 1 hour or less after the onset of symptoms at least some degree of coronary atherosclerosis could be detected¹³ as a presumably predisposing factor. However, exceptions to this rule exist. In two cases concerning young, generally healthy persons who died suddenly without any ex-

planatory antecedents or significant autopsy findings the major coronary arteries were free of atherosclerosis, but both subjects presented extraordinarily high concentrations of catecholamines in the left ventricular myocardium.^{12,14} Possible emotional factors consisted of an argument about 6 hours before death in the one case (reported after publication) and admission to a hospital also several hours before death in the other.

Disseminated necrotic and fibrotic foci resembling those which are experimentally produced by the injection of catecholamines¹⁵ have frequently been found in the subendocardium after sudden unexplained death.¹² They suggest the preceding occurrence of repeated cardiotoxic adrenergic episodes since even in complete anoxia the development of necrosis requires at least 18 minutes.¹

Interestingly, in cases of sudden unexplained death disseminated areas of potassium depletion were detected in the ventricular wall before the appearance of histologic alterations¹⁶ apparently in analogy to similar intramyocardial spotty displacements of potassium seen after the injection of epinephrine.¹⁷

Emotion induced centrally triggered acute catecholamine discharges can be assumed to play a dominant role both in the production of anginal attacks and in the causation of some types of sudden unexpected death. The observation of cardiac standstill resulting from a coincidence of vagal stimulation with discharges of vaso pressor¹²⁰ may be of significance for the explanation of sudden deaths from fright.

V Centrally and emotionally induced myocardial necroses and infarctions

Multiple necrotic foci and nonpenetrating infarctions in the myocardium of animals have frequently been observed subsequent to caustic¹¹⁶ mechanical¹¹⁷ and electrical¹¹⁸ stimulations of the central nervous system (cortex, hypothalamus, brain ventricles). The latter were accompanied by arrhythmias of apparently mixed sympathetic and vagal origin.⁹ Simultaneous electrocardiographic manifestations of myocardial ischemia were similar

to those elicited in man by head injuries or by spontaneous cerebral accidents^{119, 121} (which are followed by an augmented excretion of catecholamines¹²²) or evoked by the experimental injection of catecholamines.^{123, 124}

Intensive mechanical¹²⁵ or chemical¹²⁶ or prolonged electrical¹²⁴ stimulations of the stellate ganglia which cause an accumulation of norepinephrine in the myocardium¹²⁷ produce identical alterations of the electrocardiogram and disseminated focal necroses in the heart muscle.

The same pattern of myocardial metabolic derangements and destruction was found to occur in animals under experimental conditions in which emotional and/or sensory disturbances constituted a prominent feature such as repeated faradic shocks¹²⁷⁻¹²⁹ light flashes and noise physical restraint^{130-132, 133, 134} in rats and cage^{135, 136} or neurosis producing annoyance^{137, 138} in wild baboons (Fig. 6). Frustrating interferences in the access to food in

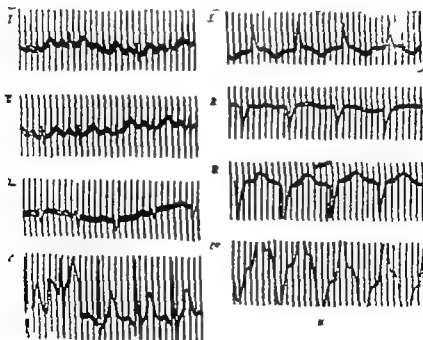


Fig. 6. Left ventricular infarction pattern in a baboon with neurosis induced by frequent hanging of light tick rhythm and feeding intervals during several months. At autopsy myocardial necroses, patent coronary arteries (from Cherk, such as Tolgorbeslav, in oligonephric, perinatal nystagmus, 6.2.1959, Medgiz Moscow).



Fig 7 Myocardial necroses produced in wild rats by anxiety (in 69 per cent of series). One week exposure to noise of tape recorded cat rat fight (From Raab et al. *Proceedings of the Society for Experimental Biology and Medicine* 116:665, 1964.)

white rats and the provocation of anxiety in gray wild rats by means of a tape recorded noisy cat rat fight¹² (Fig 7) elicited identical destructive lesions in the left ventricular myocardium.

Centrally depressing ganglionic blocking, antiadrenergic and catecholamine depleting drugs or their combination prevented the occurrence of sympathogenic myocardial necroses with different degrees of effectiveness.^{12, 13}

It should be pointed out here that in practically all of the above listed instances

of experimental centrally and peripherally elicited and emotion induced sympathogenic myocardial necroses or microinfarctions the coronary arteries were free of discernible lesions.

This seems to indicate that the excessive catecholamine discharges must have been quite massive. Analogous conditions occur in cases of pheochromocytoma which frequently causes disseminated myocardial necroses in the absence of coronary atherosclerosis.¹⁴ A prolonged duration of adrenergic overactivity constitutes a

pathogenesis aggravating element^{124, 125} Finally, the presumable participation of adrenal corticoids as a catecholamine cardiotoxicity potentiating factor needs to be taken into consideration. This will be done in Section VI.

The regularly subendocardial location of the catecholamine induced and sympathogenic foci of necrosis is probably to be explained by microcirculatory mechanisms as discussed elsewhere.^{126, 127}

The origin of myocardial lesions which have been reported as resulting from vagal stimulation¹²⁸ still remains to be elucidated.

As far as the applicability of the here described principles of centrogenic and emotion induced myocardial destruction to human pathology is concerned we have to rely—aside from the abundant indirect experimental evidence—on clinical criteria. These consist essentially in the time connection between the occurrence of emotional stimuli and significant electrocardiographic, cardiodynamic and blood chemical changes and retrospective as well as prospective epidemiologic data.

The prevalently adrenergic responses of the human heart to emotional stimuli, their documented connection with catecholamine discharges and the role of the latter in anginal attacks¹²⁷ and sudden death^{129, 130} have been discussed in the preceding sections. We have now to examine the part played by emotional and sensory stresses and irritations in the origin of structural injury to the human heart.

In doing so we will exclude from the beginning the instances of thrombotic coronary obstruction. The clinical diagnostic term coronary thrombosis has been grossly misused in the past. Today it is known that in a high percentage (up to more than 50 per cent) of clinically diagnosed infarctions no obstructing thrombus can be ascertained.^{131, 132} Moreover some investigators suspect that even detectable thrombi may constitute a secondary sequel rather than the direct cause of infarction and myocardial tissue necrosis.^{133, 134}

The possibility of a direct relationship between emotional factors and thrombus formation e.g. by way of an acceleration of blood clotting in high strung individuals¹³⁵ is still problematic.¹³⁶

The originally tempting but long-dis-

credited idea of coronary spasms as a cause of myocardial hypoxia was recently revived on the basis of apparent coronary angiographic evidence.^{137, 138} However since augmented myocardial oxygen consumption is physiologically associated with coronary dilatation rather than with constriction¹³⁹ and since cardioangiographic contrast media can temporarily reduce the coronary flow,¹⁴⁰ the possibility of artifacts caused by the introduction of such materials into the coronary arteries is not yet ruled out with certainty.

H. H. Sprague¹³⁷ has challenged the concept of a significant causal involvement of emotional stresses and tensions in the high incidence of ischemic heart disease in our civilization because stresses of various kinds have always been an inherent element of human life. This objection would have greater weight if the cardiac pathogenicity of emotional stresses were simply regarded as an isolated noxious factor by itself and not as just one additional contributory—although often decisively contributory—element within the plurifactorial framework of hypoxic myocardial (not merely coronary vascular) disease. A possible participation of emotional neurogenic elements in atherogenesis will be discussed in Section VII.

At this juncture we are dealing with the profound interference of emotionally induced disturbing neurohormonal mechanisms in a myocardium whose metabolic integrity is more often than not already threatened by other civilization dependent detriments such as diet aggravated atherosclerosis and oxygen wasting adrenergic overactivity due to a lack of exercise¹⁴¹ and/or to tobacco smoking. In other words emotional stress appears in many instances to provide only the last straw on the camel's back but as such it is to be taken seriously.

Close time connections between emotional upheavals and the occurrence of cardiac accidents are too common to require specific references beyond those listed in Section IV. The so-called anniversary infarctions precipitated by accentuated emotions on personally meaningful anniversary days¹⁴² may be mentioned as an example.

However beyond such acute corner-

dences the prolonged persistence or frequent repetition of potentially noxious emotional stimuli can be reasonably assumed to act in man as under similar model conditions in the above described striking animal experiments. The apparently high incidence of infarctions in night shift workers¹³³ may be compared to the myocardial lesions produced in baboons by alterations of the daily light and darkness rhythm.¹⁴

Several epidemiologic studies have provided suggestive evidence for an at least partial involvement of emotional stress factors in the pathogenesis of myocardial infarctions.¹⁴ Extensive statistics among American physicians¹⁴⁵ and other professional groups¹⁴⁶ revealed a distinct concordance between the degree of occupational emotional stress (e.g. among physicians the range was between the extremes of harassed general practitioners on the one hand and peaceable dermatologists on the other) and the incidence of infarctions with the exaggerated ingestion of atherogenic animal fats being recognized as an additional contributing element.¹⁴⁷

Rusman investigators^{148, 149, 150} arrived at similar conclusions comparing the cardiac ischemic morbidity among intellectuals and manual laborers not however without also calling attention to the pathogenically significant^{151, 152} difference in physical activity between these occupational groups. The same ambiguity applies to statistics from Germany¹⁵³ and India.¹⁵⁴ In this respect of interest is the fact that among the urban white collar workers in Moscow one particularly emotionally tense group, namely the highly competitive scientists, proved to be more susceptible to infarctions than did nonacademic employees.¹⁵⁵

On the other hand in a study of salaried employees within a large American industrial population¹⁵⁶ the incidence of infarction was found to be relatively low among executives presumably as a result of greater personal satisfaction and stabilization provided by having reached a high ranking secure job level.

In the so-called Western Collaborative Group Study¹⁵⁷ concerning evaluation of three cardiac risk factors, namely abnormal lipoprotein patterns, hypertension and the high strung ambitious personality

type A (which is associated with a high excretion of catecholamines¹⁵⁸ and their derivative VMA¹⁵⁹) the latter factor proved to be the most important single prognostic criterion.

A comparative freedom from degenerative heart disease observed among nomadic Somali herdsmen whose catecholamine excretion is low¹⁶⁰ and among Italian immigrants in Roseto, Pennsylvania¹⁷² (despite the massive consumption of fat by both groups) has been interpreted as suggesting a favorable influence of simple tranquil and carefree living conditions.

It must be admitted that despite their suggestive appearance the above listed epidemiologic investigations are fraught with inevitable uncertainties inherent in the difficulties of differentiation between external emotional load and individual reaction as well as due to the interference of ethnic social and unidentified somatic factors. Neither the Western nor the Roseto study results have remained unchallenged.^{161, 173}

A high cardiac sympathetic tone as expressed by a constant elevation of the heart rate and stress response seems to constitute a partially common denominator of emotional imbalance^{174, 175} on the one hand and of proneness to ischemic heart disease on the other.^{176, 177} However this presumably important factor has not yet been studied with sufficiently systematic thoroughness.

An interesting hypothesis being advanced by Mine⁷⁸ is that besides the well established cardiac detriments of emotions without motion¹⁷⁸ the opposite namely rationally motivated but not emotionally supported physical action is a feature of Western civilization may likewise interfere in myocardial metabolic health by some as yet undefined nervous mechanisms.

VI Emotions, adrenal corticoids, and myocardial damage

One particularly important emotion induced neuroendocrine phenomenon is still underexplored with regard to its probable significance in myocardial pathology, namely the augmented secretion of adrenal corticoids as an essential corollary of the well known potentially cardiotoxic

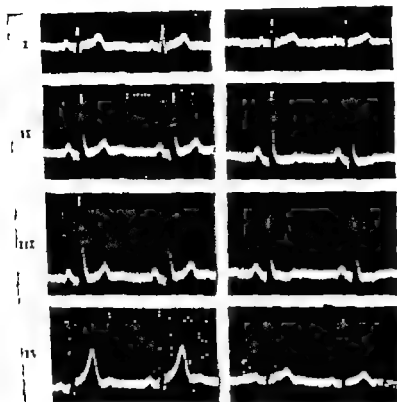


Fig. 8 Inversion of T wave (healthy) young volunteer persisting 4 weeks after injection of epinephrine following pretreatment with desoxycortosterone acetate (From Raab, *AMERICAN HEART JOURNAL* 24: 365, 1942)

overproduction of adrenergic catecholamines.^{10,11} It may be considered to be the possible cause of an even more cardiotoxic corticoid catecholamine interaction.

Selye's¹ discovery of a marked sensitization of the heart muscle by corticoids to the necrotizing cardiotoxicity of both injected catecholamines and stress induced catecholamine action¹² has been fully confirmed.^{7,13,14,15} (Fig. 8) This applies also to a corticoid induced intensification of the destructive effect of experimental local myocardial hypoxia.¹⁶ A combination of catecholamine induced metabolic hypoxia with an ACTH mediated corticoid induced superimposed loss of potassium^{17,18} from the heart muscle^{19,20,21,22,23,24} seems to constitute the underlying mechanism of myocardial destruction under stress (Fig. 9).

Physiologic studies have revealed the fact that the pituitary mediated secretion of adrenal corticoid, especially of the 17 hydroxycorticoid (17 OHCS) is aug-

mented by electrical stimulation of certain diencephalic as well as cerebral cortical areas^{25,26} simultaneously with the neurogenic liberation of adrenomedullary and sympathetic catecholamines and by similarly acting emotional central stimuli.

Increased urinary excretion or prolonged elevation of the plasma level of 17 OHCS and other corticoids were observed in animals under conditions of anxiety or aggression^{27,28} and also in both animals²⁹ and man³⁰ in response to sensory stimuli. In human beings the same occurs under various comparable emotional stresses such as situations constituting a threat to security, survival, self respect or crucial personal interrelation hips^{31,32,33,34,35,36} e.g. impending surgery, parachute jumping, long distance flying, scholastic examinations, embarrassment, interviews, sports competitions, etc.

In older persons the urinary 17 OHCS excretion seems to be generally higher³⁷

Although it was found to be low in

muscular exertion. How far this principle applies also to human beings is not yet adequately clarified.

It is known that during the night and during sleep the production of catecholamines recedes to some extent^{12,13} whereas the plasma corticoids rise between mid night and the early morning hours^{14,15} especially under prevailing stressful conditions¹⁶. This latter phenomenon may have some bearing on the problem of unexpected nocturnal deaths.¹⁷

VII Emotions, sensory stress and the vascular system

Much of the existing skepticism with regard to the pathogenic role of emotional and sensory stresses in ischemic heart disease^{18,19} is due to a widespread misunderstanding by which these stresses are alleged to be the primary or even the sole cause of severe myocardial lesions in man. It is all too often being overlooked that ischemic heart disease usually arises from a coincidence of several variable vascular and nonvascular joints contributing derangements among which stress is only one constituent albeit often a crucially important one.

The profound influence of central nervous emotional and sensory stress stimuli on the primarily nonvascular features of myocardial metabolism has been discussed in the preceding sections. Whether and to what extent such neurogenic and hormonal factors contribute also to vascular structural alterations notably to coronary atherogenesis has not yet been extensively investigated.

The possibility of markedly aggravating aortic and coronary atherogenesis through experimental interference in the central nervous system by prolonged and repeated electrical and pharmacodynamic stimulations of the hypothalamus could be demonstrated in cholesterol fed rabbits.^{20,21}

Direct angiotoxic effects of injected or secreted catecholamines or of peripheral sympathetic nerve stimulation not only concern the arterial media (so called Mönckeberg's sclerosis) but can also produce thickening and inflammatory changes of the intima^{22,23,24}. Similar apparently stress-induced vascular changes have been observed in animals.^{25,26,27,28}

In addition to direct chemical in-

fllicted on the arterial walls by their exaggerated action the catecholamines seem to contribute also to the infiltration of lipids into the intima by elevating the blood lipid level. Mobilization of free fatty acids (FFA) from adipose tissue occurs promptly under central nervous²⁹ sympathetic and catecholamine influence^{30,31} and consequently under emotional stress (chiefly fear and anger)^{32,33,34} including intensive mental effort.³⁵

The serum cholesterol level rises under provocation by central nervous stimuli^{36,37} and under emotionally stressful conditions both in animals and human beings^{38,39,40,41} even during mere anticipation of an impending stress.⁴² Differences between the basic serum cholesterol level of high strung and irritable persons on the one hand and that of placid easy going ones on the other⁴³ were however not observed with regularity.^{44,45}

Serum triglycerides were found to be augmented in some excitable individuals⁴⁶ under stress.^{47,48}

On the basis of the hypothesis that catecholamine mobilized free fatty acids are transformed in the liver into triglycerides and phospholipids⁴⁹ one may suspect a sympathetic triggered mechanism participating in the origin of potentially atherogenic hypercholesterolemia. This would represent the opposite of the beneficial reduction of both the sympathetic tone and the serum cholesterol level by physical training.⁵⁰ It would further resemble the blood glucose elevations under stress and sympathetic activity on the one hand⁵¹ and the frequently increased blood glucose level of coronary prone individuals⁵² on the other.

These apparent blood chemical interrelationships suggest one more possible dimension of potentially cardiovascular sympathetic overactivity involving not only the myocardium itself but also the latter's supplying coronary arteries via interference in lipid metabolism.

Finally arterial hypertension has to be considered to be a partially neurogenic, partially hormonal and often emotionally aggravated cardiac risk factor.

Elevations of the diastolic pressure impose an increased mechanical load on the heart muscle and contribute to a hypo-

ating hemodynamic compression of the left ventricular subendocardial arteries.¹⁹⁻²¹ This becomes all the more critical if myocardial oxygen consumption is augmented by simultaneous sympathogenic local catecholamine action.

Causal connections between central nervous stimulation, emotional excitement, attitudes of hostility, frustration and tensions on the one hand and acute or sustained elevations of the blood pressure on the other have long been recognized.²²⁻²⁴ They are particularly emphasized by the Russian school of thought.²⁴

Sensory stresses such as noise and light stimuli can likewise produce transient or prolonged hypertensive reactions in animals²⁵⁻²⁷ and man²⁷⁻³⁰ (Figs 2 and 3).

In pluricausal so called essential hypertension at rest the level of catecholamines in the plasma does not usually exceed normal limits.³¹⁻³³ Mineralocorticoid action probably by affecting vascular electrolyte metabolism³⁴⁻³⁶ increases the arterial contractile response to catecholamines.³⁷ Whether the irregularly observed augmentation of aldosterone production in essential hypertension³⁸ can be attributed to emotional factors remains in doubt.

Finally, high levels of blood pressure seem to contribute to atherogenesis³⁹ and thus may constitute an additional possible pathogenic link between emotional stresses and myocardial damage.

VIII Emotional stress and congestive heart failure

Emotional stresses have to be considered as factors contributing both to catecholamine and/or corticoid induced direct myocardial damage and to elevations of the blood pressure all of which may lead separately or jointly to congestive heart failure especially in the presence of coronary atherosclerosis or valvular lesions.

The capacity of augmented catecholamine action to elicit left ventricular failure and pulmonary edema^{2, 3} has been demonstrated many times by the injection or infusion of epinephrine, norepinephrine⁴⁰⁻⁴² or isoproterenol⁴³ and by the common occurrence of death from con-

gestive heart failure in patients with pheochromocytoma.⁴⁴⁻⁴⁶

Equally common is the development of congestive heart failure in cases of adrenocortical tumors.⁴⁷ Augmented fatal catecholamine cardiotoxicity has been observed under spontaneous corticoid overaction as it occurs in rats under the influence of prolonged isolation.⁴⁷⁻⁴⁹ Thus an excess of catecholamines as well as of corticoids, a joint overproduction of both of which is a characteristic manifestation of emotional stress ranks manifestly among the causative or aggravating mechanisms in congestive heart failure presumably due to combined hypoxiating catecholamine and potassium depleting corticoid action (see Section I f).

Signs of congestive failure developing under emotional stress have been observed also in anthropoid apes.⁵⁰⁻⁵²

Certain metabolic alterations found in the failing myocardium closely resemble those which are typically produced by exaggerated catecholamine interference.¹⁷⁻¹⁹ However in the already damaged failing human heart muscle the norepinephrine content is reduced⁵³⁻⁵⁵ whereas epinephrine tends to be increased.⁵ The reason for these changes is not yet clear but they can scarcely invalidate the concept that initially an emotion induced overproduction of catecholamines may have played an important role in many instances in inducing the myocardium before the latter went into failure and secondarily lost part of its norepinephrine stores.

In the majority of a recorded series of clinical cases of congestive heart failure chronic emotional difficulties as well as acute conflicts appeared to represent a significantly precipitating element.⁵⁶ This was substantiated by the observation that in such patients deliberately induced acute emotional and mental stresses provoke a rise in central venous pressure.⁵⁶

The sensory stresses of heat and humidity are likewise apt to elicit adrenergic hemodynamic and cardiac manifestations and to markedly aggravate an existing state of congestive heart failure.⁵⁷

Some of the alterations in electrolytes, phosphates, proteins, enzymes etc. which are detectable in the failing heart muscle⁵⁸⁻⁶⁰ probably represent secondary

sequelae of pre-established myocardial lesions rather than specific primary derangements of neurohormonal and hormonal origin.

The overproduction of aldosterone, an other characteristic feature of the congestive failure syndrome may likewise be interpreted as a secondary complicating phenomenon.^{11, 12}

IX. Emotion and sensory oriented therapy and prevention

Therapy will be discussed here only in so far as it is aimed at the reduction of emotion and sensory induced central nervous overstimulation and at the resulting overproduction and overactivity of cardiovascular catecholamines and corticoids.

Beyond protection of the patient from emotionally strenuous situations annoying noises, glaring or unsteady light and uncomfortable atmospheric temperature and humidity, the application of specific drug treatment is indicated according to circumstances.

Animal experiments have shown that the development of stress induced^{13, 14} or peripheral sympathetic stimulation induced¹⁵ myocardial necrosis can be prevented by treatment with centrally tranquilizing^{13, 16} peripherally ganglionic blocking¹⁷ catecholamine depleting¹⁸ and adrenolytic^{19, 20} drugs. It appears that tranquilizing drugs are more effective in controlling sympathetic neurosecretory than adrenal cortical overaction.²¹

Emotionally induced and mental stress induced cardiac accelerations can be counteracted by beta adrenergic blockers^{22, 23, 24} and monoamine oxidase inhibitors²⁵ which are believed to inhibit ganglionic and postganglionic transmission.^{26, 27, 28}

Angina pectoris, the classic example of emotion and catecholamine provoked acute myocardial hypoxia in the presence of coronary atherosclerosis²⁹ can be ameliorated or caused to disappear by a variety of intradrenergic measures: vasotropic and sympathoinhibitory³⁰ carotid sinus pressure during the attack,³¹ catecholamine reactivity reducing and sedating anti thyroid treatment,³² adrenomedullary activity suppressing roentgen irradiation of the adrenal glands,³³ cardiac sympathet-

omy³⁴ tranquilizers such as meprobital^{35, 36} and others^{37, 38} monoamine oxidase inhibitors³⁹ beta receptor blockers⁴⁰ and a new apparently plurifunctional drug Segontin.⁴¹

Probably the most powerful antiadrenergic and myocardial oxygen economy restoring, preventive and rehabilitative measure is cautiously progressive but ultimately vigorous regular physical activity. It gradually lowers the exaggerated cardiac chronotropic and inotropic sympathetic tone of sedentary and tense individuals and raises the oxygen preserving vagal tone.^{42, 43, 44, 45} In ischemic areas of the heart muscle it promotes the development of collaterals.⁴⁶ Moreover animal experiments by Selje⁴⁷ and Brjuzs⁴⁸ suggest that repeated exercising contributes to the accumulation of an augmented protective reserve of potassium in the myocardial tissue whereby neuroendocrine mechanisms are presumably involved.⁴⁹

The emotionally equilibrating effects of regular exercising are well known⁵⁰ and so are the psychological benefits of post infarction physical rehabilitation.⁵¹

Combinations of periods of environmental emotional relaxation with physical training and with the inculcation of permanent sensible health habits have been systematically organized in Europe over the last four and a half decades on a very large scale in about three thousand rural reconditioning centers. These are located mostly in attractive serene mountainous areas and accommodate annually about five million fatigued and tense pre patients and patients for physical and emotional reconditioning. Some of these centers offer instruction in handicrafts and other hobbies for creative emotionally satisfying utilization of leisure time.^{52, 53}

Studies from European centers have revealed a nearly uniformly improved subjective well being of the trainees and 4 to 6 weeks of combined environmental emotional and physical reconditioning have also been followed by a measurable diminution of the cardiac sympathetic tone. This was manifested chiefly by a slower heart rate at rest and during exercise^{54, 55, 56} and by a prolongation of the isometric period of the left ventricle^{57, 58} which persisted for periods of several months to over 1

year.²² The blood pressure responses to standard exercise were likewise frequently reduced.^{23,24} In the majority of persons with signs of ischemic heart disease the electrocardiogram at rest and/or during exercise and the ballistocardiogram were improved or normalized and the serum cholesterol level was lowered.^{25,26}

It seems to be probable that the emotionally appealing rural and mountainous environment of these centers exerts its beneficial influence in a way related to the decrease in the production of catecholamines²⁷ and 17 hydroxycorticosteroids²⁸ which was observed during the viewing of scenic nature films.

Experience in the reconditioning centers has shown that the strong emotional impact of an extended close exposure to natural pleasant surroundings and the gain in self confidence after improvement in physical fitness make the trustees particularly amenable to the acceptance and maintenance of indefinitely continued health habits.

X Conclusions

An up to date insight into the complex problem of emotion and sensory stress induced derangements of myocardial function and structure requires coordination and integration of numerous splinter data from the international literature pertinent to the divergent disciplines of biochemistry, physiology, neuroendocrinology, pharmacology, pathology, clinical medicine, psychology, epidemiology, and sociology.

In spite of inevitable omissions and a multitude of still unresolved questions with regard to details the foregoing attempted review of present day knowledge warrants the definite conclusion that emotional and sensory stress factors are directly responsible as contributory if not exclusive causative elements in such myocardial abnormalities as tachycardia, various arrhythmias, electrocardiographic changes of the hypoxic type, anginal attacks, sudden unexpected death, subendocardial disseminated micronecroses (sometimes confluent into larger non transmural infarctions), myocardial fibrosis, and acute or chronic congestive heart failure with or without pulmonary edema.

Experimental and clinical evidence has made it clear beyond reasonable doubt that cerebral cortical and subcortical emotional and sensory stimuli particularly anxiety and anger elevate the sympathetic tone and thus initiate the local liberation of norepinephrine within the myocardium and epinephrine from the adrenal medulla. Both of these catecholamines augment myocardial oxygen consumption. In the absence of adequate compensatory dilatability of the coronary arteries or in the case of exhaustion of even the normal coronary reserve,¹ injurious anoxia will occur in the most directly affected cell groups of the heart muscle notably in the hemodynamically compressed subendocardium. Emotionally triggered simultaneous rises in peripheral vascular resistance are apt to impose an additional mechanical load on an already metabolically handicapped myocardium.

A still inadequately explored but presumably highly important role of involvement of the adrenal cortex in emotion and sensory stress induced myocardial pathology is emerging from recent studies. These have revealed a striking parallelism between the central nervous regulation of adrenergic catecholamine liberation and the secretion of 17 hydroxycorticosteroids and other steroids from the adrenal cortex. In view of the marked intensification of catecholamine cardiotoxicity by adrenal corticoids^{11,12,29,30,31,32,33,34} and of the simultaneous overproduction of both myocardial hyperventilating catecholamines and myocardial potassium depletion,⁶ corticoids under emotional stress^{35,36} (Fig. 9) further investigation of this challenging problem of cardiac pathogenesis appears to be most promising. (Interestingly in contrast to emotional arousal the even more marked sympathetic stimulation during physical exercise is not associated with an increased secretion of adrenal corticoids and accordingly seems to be less cardiotoxic.)

The common denominator of cardiotoxic catecholamine and corticoid action in myocardial metabolism is to be sought in the specific mutually aggravating influences exerted by both of these hormone categories upon local potassium and sodium exchange.

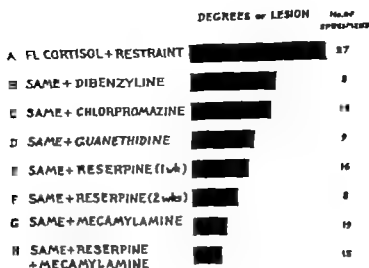


Fig 10 Degree of stress plus corticoid induced myocardial necrosis in rats (black bars) reduced by antiadrenergic premedication (From Raab et al. *American Journal of Cardiology* 8:203 1961 by permission)

Whether and to what extent emotional and sensory stress factors have a part in coronary atherogenesis possibly by way of raising the serum cholesterol level remains a moot question.

The logical therapeutic approach to clinical cardiac manifestations of at least partially emotional origin consists apart from frank psychotherapy in a reduction of exogenous emotion and sensory induced central stimuli (with tranquilizers, hypnotics) and/or the use of peripherally acting antiadrenergic medication (ganglionic blockers, catecholamine desensitizing thyrostatic agents, beta receptor blockers, catecholamine depletors and adrenergic drugs) (Fig 10).

Early pre-morbid prevention is theoretically and practically feasible by the adoption of a serene not overly competitive outlook on life problems, choice of a physically and emotionally appealing environment at least periodically, and a creative subjectively satisfying utilization of leisure time.

However, it is imperative to keep in mind that in the same way in which degenerative hypoxic heart disease is plurifactorial and not attributable to one single category of pathogenic factors, prevention must be carried out equally pluridirectionally.

In a somewhat simplified fashion it has

to be aimed at (a) diet promoted coronary vascular disease and (b) the exaggerated neurogenic metabolic vulnerability of the myocardium which is caused by the adrenergic triad of jointly or singly contributing lack of exercise, tobacco smoking and emotional plus sensory stresses in varying distributions and degrees.

XI Summary

In the complex but increasingly perceptible plurifactorial pathogenesis of degenerative (so called coronary) disease of the heart muscle emotional and sensory stresses play a prominent even though usually only contributory role.

Scrutiny of the pertinent contemporary transdisciplinary world literature provides abundant experimental and clinical evidence for a potentially cardiotoxic overproduction of sympathogenic catecholamines and adrenocortical steroids resulting from emotional and sensory stress induced stimulations of the central nervous system and the pituitary gland.

Fear, anger and frustration as well as to a lesser extent optical, acoustical and thermal annoyances act as the most common potentially pathogenic stimuli.

These stimuli disturb via the sympatho-adrenomedullary system the oxygen economy of the myocardium (particularly in conjunction with preexisting coronary

atherosclerosis and with the often associated additional adrenergic manifestations of physical inactivity and of nicotine). Intramyocardial electrolyte shifts due to catecholamine induced local hypoxia and superimposed corticoid induced depletion of myocardial potassium may be assumed to constitute the most fundamental metabolic derangements involved.

There is only sparse evidence in favor of a significant contribution of emotional and sensory stimuli to coronary atherogenesis. However stress induced sympathetic and adrenal cortical overreaction seems to affect the myocardium also in directly by way of elevations of blood pressure and resulting hemodynamic strain.

Prevention and counteraction of emotional and sensory detriments to the myocardium are feasible through psychotherapy, environmental adjustments, physical reconditioning and tranquilizing and/or directly antidiadrenergic medication.

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Appraisal and reappraisal of cardiac therapy

Edited by Arthur C DeGraff and Alan F Lyon

Reappraisal of digitalis Part II

Hemodynamic effects of the cardiac glycosides

Alan F Lyon MD

Arthur C DeGraff MD

New York NY

That digitalis can produce marked improvement in some patients with congestive heart failure is a well known fact. There is, however, disagreement as to the particular situations in which it is most effective. Is it as effective in the presence of normal sinus rhythm as with atrial fibrillation? Is it equally effective in heart disease of all etiologies? Does it have any effect in the presence of compensated heart disease or in the normal heart? Furthermore, there has been confusion as to the mode of action of digitalis in heart failure. It has been variously proposed that it exerts its effect by a direct diuretic action on the kidney, by a reduction in the venous return to the heart, or by an increase in the force of contraction of heart muscle. In recent years the development of cardiac catheterization and other modern recording techniques has led to the resolution of many, although not all of the problems.

Range of effectiveness. It is now clear that in most patients with congestive heart failure digitalis will lead to a reduction in mean atrial pressures and in ventricular end diastolic pressures to a rise in cardiac output, diuresis, and clinical improvement, whether the patient is in atrial fibrillation or normal sinus rhythm.

Although this effect is most striking in the low output failure of arteriosclerotic, hypertensive and aortic valvular disease, the drug has been demonstrated to be effective in mitral valvular disease, pulmonary heart disease and primary myocardial disease, and even acute rheumatic carditis, in which case its value had often been doubted on clinical ground. It has also been shown that there are patients apparently similar to those in whom digitalis is markedly effective, in whom digitalis has little effect on cardiac pressures and output, or in whom it can accomplish no more than diuretic therapy. How these patients differ from the larger group is still not clear.

Effect on contractility. The most important factor in the improvement of heart failure is an increase in the contractility of heart muscle, that is an increase in both the speed and force of cardiac contraction. Direct proof of this increase in the force of cardiac contraction has been obtained not only in isolated heart muscle preparations, but also in human subjects. In the latter instance this has been demonstrated by the use of open heart surgery of the Walton-Brodie strain gauge arch, which can record isometric tension in an exposed portion of the heart.

ing heart. This technique has consistently shown the development of an increase in tension after digitalis whereas the more indirect analysis using the relationship of ventricular end diastolic pressure and stroke work has not always done so probably because of compensatory reduction in sympathetic tone.

The other aspect of contractility, the speed of contraction can be assessed by the rate of rise in ventricular pressure. This is most accurately measured as the first derivative of the first portion of the ventricular pressure curve (dp/dt). This measurement is markedly increased after the administration of digitalis which gives further evidence of the favorable effect of digitalis on contractility.

It is this increase in contractility that leads to more complete emptying of the ventricle, clearing of venous congestion, fall in venous pressure and increased cardiac output. This action is adequate to account for most of the effects of digitalis in heart failure but the total effect of digitalis is more complicated.

Effects on venous circulation. It appears that there is an independent and substantial effect of digitalis on the venous bed which leads both in animals and in man to a reduction in venous return. This along with improved ventricular function contribute to the observed fall in central venous pressure.

Measurements of venous pressure volume in the forearm and in the splanchnic bed suggest that the effect of digitalis is one of venoconstriction. In the dog, the fall in venous return despite increased venous tone is explained by constriction of the hepatic veins which dams blood in the portal circulation and raises portal pressure. In man constriction of the hepatic veins does not appear to be adequate to explain the diminished venous return that does occur and the exact mechanism is unknown.

Effect on diuresis. A renal action of digitalis has been demonstrated experimentally. Digitalis inhibits the renal reabsorption of sodium probably by the same mechanism by which it interferes with the transfer of sodium and potassium in cardiac cells; this effect is quantitatively unimportant at therapeutic levels. Digitalis

does cause a diuresis but it does so by improving primarily cardiac and secondarily renal function. Significant diuresis can occur before there is a clear cut increase in renal blood flow or glomerular filtration but these are not the only factors affecting renal function in heart failure. It is likely that this early diuresis is due to a change in some other aspect of congestive heart failure perhaps hormonal rather than to a direct effect of the drug on the kidney.

Effect on the normal heart. It was suggested in the past that digitalis might be deleterious to the mechanical function of the normal heart. It has been noted that there was often a reduction in the size of the normal heart after digitalis therapy and it was postulated that by increasing ventricular tone digitalis reduced the capacity of the ventricle and thus the cardiac output. More recent studies have shown a variable effect of digitalis on the output of the normal heart; some investigators find no change and others find a slight reduction in cardiac output. This reduction in resting output if it is present would appear to be of little significance since the response to exercise is unchanged from the normal. Most important the increase in force and speed of contraction that digitalis induces in a heart in congestive failure also occurs in the normal heart. Such an increase in contractility is of no importance in the normal subject in whom the basic line contractility function of the heart is adequate to handle the blood returned to it. When a fall in basal cardiac output does occur in a normal subject given digitalis it can be attributed to a reduction in venous return produced by the same mechanisms operative in the mitigation of congestive heart failure.

Effect on peripheral arteries. Digitalis produces a rise in peripheral resistance due to arteriolar constriction. The effect in the normal subject is more easily demonstrated than in the presence of congestive heart failure which itself causes a rise in peripheral resistance. As digitalis relieves congestive heart failure the stimulus to constriction is reduced and the net effect is often one of arteriolar dilatation opposite to the direct effect of digitalis. The direct effect of digitalis on the arteriolar bed is

a local one since it can be demonstrated to occur despite ganglionic blockade and with local perfusion.

Just as digitalis can increase the contractility of the normal heart so it can increase the contractility of the hypertrophied heart without failure. Such an increase in contractility is of no value to the normal subject whether it is of value to patients with compensated heart disease is in doubt. In such patients the usual indices of pressures and outputs at rest and exercise are not modified. It has been reported however that the oxygen debt accumulated by such subjects on exercise is reduced. Animals whose ventricles are stressed by aortic constriction develop less hypertrophy when they are maintained on digitalis. Because of the multiple and complex effects of digitalis in addition to that on contractility the usefulness of digitalis in compensated heart disease must at present be decided on clinical rather than hemodynamic grounds.

The major effect of digitalis in heart failure is on contractility. Measurement of contractility by strain gauge dp/dt and more indirect measures such as shortening of the rate corrected systolic ejection time and shortening of isovolumic contraction (the period from the onset of contraction to the opening of the semilunar valves) has shown that the effect of digitalis on contractility is not all or none but stepwise. Increasing doses of digitalis up to a point will produce increasing augmenta-

tion of contractility. This observation has important bearing on the traditional concepts of the loading and maintenance doses of digitalis.

Summary. The administration of the cardiac glycosides will result in a reduction in filling pressures, increase in cardiac output, diuresis and symptomatic improvement in most patients in congestive heart failure irrespective of cardiac rhythm. Although they exert direct effects on the peripheral arterial and venous bed and on kidney function the improvement in heart failure that the cardiac glycosides produce is due primarily to an increase in contractility of ventricular muscle. The degree of increase in contractility is related to dosage in the therapeutic range.

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serum cholesterol during the acute attack. They found it difficult to interpret these findings.

To date no satisfactory explanation of the pathogenesis of acute gouty arthritis has been offered. Wolfson and Robinson have suggested that the acute attack of gout is principally of vascular origin. The decrease in serum cholesterol as well as in serum uric acid during the acute attack may be the result of deposition of these substances in the vascular wall or they may be utilized in the formation of atheroma.

The occurrence of cerebral infarction and acute gout cannot be accepted as concrete evidence of a causal relation but the consideration of such a possibility seems to be justified. An attractive postulate for the occurrence of the two disorders in the same individual seems to be that cerebral infarction and gout may be manifestations of the same basic metabolic state in which the cardinal feature is hyperuricemia.

The fundamental problems of cerebral infarction are those of atheroclerosis. Despite the vigorous and prolific efforts that have gone into the study of atherosclerosis during the 50 years since Wautchlow succeeded in producing atherosclerosis in cholesterol-fed rabbits we know very little about the etiology and pathogenesis of atherosclerosis. Evidence accumulating that atherosclerosis represents a metabolic disorder involving particular lipids but a final proof of a causal relationship has as yet not yet been established. It is possible that hypercholesterolemia as well as atherosclerosis may represent manifestations of an altered metabolic state.

The association of gout and arterio-sclerosis has been a clinical concept since the end of the last century. Roberts declared the importance of the uric acid of atherosclerosis for the development of thrombotic phenomena and Huchard¹⁴ wrote "l'artériosclérose et l'hyperurémie sont deux choses certaines sur les seules manifestations de cette diathèse. The subject of gout was forgotten or dropped in the beginning of this century" and the association of gout and arterio-sclerosis is faded as well. Although gout is a widely fairly related to gout of the great antiquity, it is not to be one of the last thought of by the clinician.

The evidence that uric acid has a deleterious effect on the arteries is very meagre.

During the last decade occasional interest was expressed concerning hyperuricemia in degenerative vascular disease. A postulated relation between hyperuricemia and coronary artery disease was documented by Hume and associates¹⁵ found by percutaneous coronary catheterization that the degree of involvement seemed to be related to the degree of elevation of uric acid.

In a series of 53 cases of cerebrovascular disease there were 19 (35 per cent) in which hyperuricemia was present. The authors demonstrated the possibility that the elevated level of serum uric acid were the result of cerebral infarction on the basis of the fact that only 3 of the 19 patients had recent cerebral infarction and 3 of these 3 had a previous history of long-standing gout.

In a survey of serum uric acid in 66 males and 49 females with acute cerebral infarction hyperuricemia was found in 17 males and 4 females (36 per cent).¹⁶ None of the patients had prior to the analysis of uric acid received drugs with hyperuricemic properties. All of the determination of uric acid were carried out with enzymatic photometry developed by Hachlar, Pyrronius and Pyrronius and Posten.¹⁷ Six of the patients had a previous history of gout. It seems to be unlikely that the observed elevation of serum uric acid is related to the presence of stress or renal failure or to a abnormal cellular breakdown. A follow-up examination averaging 13 months after the initial stroke revealed hyperuricemia in 15 (34 per cent) of the 64 patients examined despite the fact that some of the patients had been given treatment with uric acid drugs.

These studies support the clinical impression of a relationship between gout and atherosclerosis disorders.

There is a bulk of evidence of a relationship between the metabolism of purines and that of lipids. Since Hutchison in 1889 in the Clinical Society of London related a case of uricemia and gout in a 44-year-old Hebrew there have been several reports concerning the occurrence of hyperuricemia and hypercholesterolemia. High level of serum uric acid are frequently encountered in essential hypercholesterolemia and conversely a high level of plasma cholesterol is often found in patients with gout. The reader is referred to a review of the literature concerning this subject.

In my series of 115 patients with cerebral infarction 14 patients revealed hyperuricemia as well as hypercholesterolemia. The value 3.2 Gm per liter is taken as the upper limit of normal of cholesterol (unpublished).

Further evidence of a metabolic relation between blood cholesterol and uric acid was demonstrated by Edlitz who found that blood cholesterol was strikingly lowered by penicillin. A decrease in blood cholesterol has also been observed after the administration of xanthine oxidase. Both the drugs have a xanthine effect.

It is established that a high fat diet results in an increase in uric acid in the blood and therefore an amount of the substrate for the uric acid (gout) and normal subjects.

The report of Tait and associates¹⁸ on specific vascular lesions in patients with gout supports further the hypothesis of therapeutic effect of uric acid. So does the observation of Oler who from his wide autopsy and clinical experience noted the frequency of arteriosclerosis and cardiac hypertrophy in gouty patients. He noted that patients with gout had a high incidence of uric acid associated infarction in the myocardium and arteriosclerosis, chronic interstitial nephritis and changes in the myocardium.

Scriver and associates¹⁹ showed that patients with gout had increased blood uric acid levels. Terms of platelet turnover and platelet aggregation were also studied in the platelet activity. The study of uric acid metabolism in atherosclerosis. Interestingly related to uric acid.

longed and platelet turnover decreased during salicyrins (Anturin) therapy. There was a corresponding fall in platelet count and decrease in platelet adhesion.

The predominance of female over males in the study concerning uric acid levels in acute cerebral infarction supports the view that the atherogenic effect of hyperuricemia and gout because of the rarity of gout in women. It seems to be trivial but nevertheless important to emphasize that gout and hyperuricemia are not interchangeable terms. Only 20 per cent of individuals with hyperuricemia will develop articular symptoms. The rarity of gout in females does not exclude nonarticular hyperuricemia in this sex.

The frequent occurrence of hyperuricemia and degenerative diseases in the same individual does prove a relationship but does appear to be more than a mere coincidence. An exact interpretation of this finding must be deferred. It may be postulated that hyperuricemia, hypercholesterolemia and atherosclerosis represent manifestations of the same metabolic state. Hyperuricemia will cause haemic gout in those disposed by heredity and it is suggested that similar phenomena occur for the acute attack of gout.

This hypothesis raises important questions. Does treatment with uricosuric drugs prevent atherosclerosis in hyperuricemic individuals? Is the potent uricosuric effect of certain antihypertensives of a therapeutic significance in individuals with hyperuricemia and atherosclerosis? Manifestation and the effect of Anturin on platelet economy of atherosclerosis in preventing the development of the latter in gouty subjects. Does all the incidence of atherosclerosis in a patient with gout remain to be determined?

*Dr Enaid H. Nasser, M.D.
Department of Neurology
Copenhagen County Hospital
Glostrup, Denmark*

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demand it of us and so we go on vying with each other for incumbency of excellence (see for example the figures on books published by Oxford, Cambridge and Berkeley, *Academica* is the Franks report 1966).

Those who derry must also expound and it would be no business to critique without attempting to point the way to better things. The fault lies not so much in the concept of the textbook but in our misinterpretation of it as more than a personal expression or analysis of a body of fact. If it remains the latter as distinct from an attempt to become a means of conveying subject totally and permanently then it is still a living and dynamic thing. If it is merely to be a card index then it would be better stored in a computer or written as a dictionary or encyclopedia. Unfortunately textbooks and the textbook style have degenerated since Winslow published in 1732 his *Exposition of Anatomy* which set a standard of clarity and verbal economy that swept away the fog of overornamented discourse and avoided constructions which to use his own word might have been most pleasing to a reader of a light and classical taste. There seems unfortunately to be a return to such elaborate and decorative prose perhaps because the study of language as a means of communication is passing into too self-conscious a phase.

If we must fly from the turgidity and inadequacy of textbooks and seek for better means of expressing ourselves in an engaging manner we must not forget that other things such as the free exchange of information may also be lost. The dissemination of information is a curious and strangely enough to the R.C. a unique situation of personal exchange of views between centres of savants. In zoology, immunology, nephrology, and doubtless cardiology, ideas are now exchanged through conferences, the circulation of papers and advance notices of publication. Although this is a most admirable situation it has the danger first the possibility of a reduction of abnormal situation in which one is so well informed (everyone else's work as to be quite inhibited from doing any oneself seriously, the serious risks of transcribing and transmitting degeneration as manuscripts whirled around the world and

are summarized, abstracted and misquoted thirdly the further multiplication of both papers and journals for facts rather than ideas. Thus these new societies in close but restricted personal communication are but a partial solution and a danger in that they do not provide for the uninitiated or give rise to a service to teachers or to learners. More may be achieved by the periodic narrowly directed conference which has as its prime objective the adoption of certain ideas, concepts or definitions. Our new textbooks may thus come to be written by consensus and as reports of such gatherings. They need not consequently be catechism as indeed the relatively fiery proceedings of one such recent meeting show. It will I believe be increasingly the task of Societies, Institutions and Journals such as the *AMERICAN HEART JOURNAL* to work out such transiently authoritative but living statements of learning for the textbook as by the nature of events no longer able to provide.

H. A. P. Dudley Ch. M. F.R.C.S. F.R.I.C.S.
Department of Surgery
Monash University
Victoria Australia

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DISEASES OF THE HEART By Chark H. Friedberg M.D. ed 3 Philadelphia 1966 W. B. Saunders Company 1787 pgs. Price \$27

Dr. Friedberg rendered an excellent and much needed service to clinical medicine and cardiology when he published the first edition of his book. The third edition makes this book *success*. It continues to present cardiology in a practical clinical manner and at the same time includes the basis of the disease and associated pathophysiology. A fairly complete bibliography is appended to each chapter thus making the book a good reference source. The increased size of the book reflects the growth of knowledge in the field of cardiology. This is a good, clearly written book which should be owned by all cardiologists and internists who do a major practice in cardiology. Dr. Friedberg has managed extremely well in keeping his excellent book up to date.

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selected to write the many chapters are able clinicians who therefore have presented the data for the practicing physician and the student learning medicine. The presentations are brief and lucid. This reference book will be appreciated by many doctors, and especially those with a busy practice.

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3. H.D. New York 1966 Hoeber Medical Division (Harper and Row) 1500 pages per year. Price \$16 per year.

Announcements

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Delegates wishing to attend the Post Congress Session in Bombay should contact Dr. B. N. J. Pinto, Organizing Secretary, Experiance Club, Cama Hospital, Bombay 1 India.

A SEMINAR ON DIGITALIS AND THE HEART will be presented Oct. 15 and 16 1966 at the DeGoes Memorial Hospital, Burlington, Vermont sponsored by the Vermont Heart Association and the University of Vermont in collaboration with the American College of Cardiology. Programs may be obtained from Eugene Lepachkin M.D., Cardiovascular Research Unit, DeGoes Memorial Hospital, Burlington, Vt.

Editorial

The fallacy of the Bainbridge reflex

C L Palhak M B B S M D Ph D (Glas)*

Ldaipur India

The reflex regulation of the cardiovascular system is well known. These reflexes arise mainly from various sensing structures (sensory receptors) located in the cardiovascular system itself.^{1,2} The pressure receptors located in the carotid sinus and aortic arch and at other sites in the arterial tree play the main role in the homeostatic control of blood pressure and cardiac action. Besides the reflexes arising from the extracardiac baroreceptors and chemoreceptors there is an important group of reflexes originating from the heart itself. Among these reflexes one of the commonly accepted reactions has been the Bainbridge reflex or right atrial reflex which has been receiving the attention of authors of various textbooks of physiology. As Philip Bard³ says this reflex is better known to medical students than any other circulatory reflex. It has been considered to be an important cardiovascular homeostatic mechanism responsible for the regulation of heart rate.

Professor Bainbridge conducted his experiments on anesthetized dogs and showed that intravenous infusions of saline or blood resulted in an increase in the heart rate. This infusion acceleration response was found to be reduced by atropine and abolished by vagotomy. The conclusion

was that the infusion raises the intra-atrial pressure and stimulates some stretch receptors from which nervous impulses ascend to the medullary centers where they lead to a reduction in tone of the vagus and also presumably influence the heart rate by simultaneously stimulating the cardioaccelerator center.⁴ Thus the increase in the heart rate was attributed to readjustments in the autonomic activity reflexly through the medullary centers. This infusion acceleration response was called Bainbridge reflex.

During the past 50 years a number of workers using various techniques have investigated this reflex. The universality of infusion acceleration response has not been confirmed nor has any evidence of its being a reflex effect been forthcoming.

DeGriff and Sands⁵ noted acceleration in only 50 per cent of cases but vagotomy was not always effective in abolishing the reflex. Aurep and Segal⁶ obtained acceleration frequently but not always in innervated heart lung preparation. They suggested that it was premature to consider an increase in the central venous pressure as the stimulus for the reflex. Ballin and Katz⁷ did not induce acceleration in anesthetized dogs but in unanesthetized dogs they could induce acceleration when either

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of pulmonary deflation receptors has also been established.²⁰ Hypotension and bradycardia follow stimulation of them. It must also be admitted that intravenous infusions are likely to increase the cardiac output and blood pressure and the resultant baroreceptor activity is likely to increase the vagal tone instead of decreasing it. Thus reflex cardiac acceleration if it is to occur must occur despite the presence of such a formidable number of opposing cardiopulmonary reflexes all of which could be brought into action simultaneously by an increase in the venous return.

Many other considerations rule out nervous interference in the infusion acceleration response. The stretch receptors or the neural pathways believed to be concerned with the Bainbridge reflex have never been demonstrated by any worker although a large number of workers devoted considerable time and effort to isolating the receptors and their nervous connections (Jarusch and Zotterman²¹ Avidado and Schmidt² Heymans and Neil²² and many others). Electrophysiologic recordings of single fiber potentials have also failed to demonstrate any such structures or connections.²³

The foregoing discussion clearly indicates that the Bainbridge reflex never had any sound basis. Acceleration of heart rate is not a constant accompaniment of intravenous infusion. In a few instances in which it has been observed no unequivocal evidence has been produced to show that it is a reflex effect. In fact one cannot think of a reflex behaving in this fashion, i.e. operative in some animals and not in others and even operative in the same animal in one trial and not in another under the same experimental conditions. However an analysis of the work of various investigators yielded the following conclusions:

1. There was very little evidence to substantiate the view that the infusion acceleration response had a reflex basis.

The term Bainbridge reflex persisted in the literature despite many shortcomings because it had been so firmly entrenched in the minds of respectable teachers. It is being perpetuated from textbook to textbook by distinguished authors even in recent years frequently with such arguments that it would be a

nice thing or with the unfounded hope that better techniques in the future may be useful.

3. The infusion acceleration response did occur in some trials in some animals.

4. The heart rate might increase or decrease or remain unaltered as a result of intravenous infusion.

5. An initial low heart rate was conducive to the production of the infusion acceleration response and vagotomy was frequently effective in abolishing it.

6. Some alternative explanation had to be furnished for the occurrence of chronotropic effects when the intra-atrial pressure was raised.

The real explanation of the greater chances of obtaining the infusion acceleration response when the initial heart rate was low (i.e. the vagal tone was high) or when the vagi were intact had been furnished by Titus²⁴ as long ago as 1937. Titus showed that the cardioacceleratory response to infusion was abolished by vagotomy not because of elimination of the afferent or efferent limb of the Bainbridge reflex but because right vagal section increased the heart rate almost to its maximal level. He showed that the infusion acceleration response could be obtained even after vagotomy if the heart rate were slowed by artificial stimulation of the peripheral end of the sectioned right vagus nerve. It appears that in the interest of preservation of the concept of the Bainbridge reflex Titus's work was completely overlooked and neglected.

In an effort to find an alternative explanation for the infusion acceleration response I decided to extend the work on chronotropic changes in isolated hearts. A detailed systematically planned study was therefore undertaken on isolated whole hearts and their individual chambers under critically controlled experimental conditions. This work on isolated frog whole hearts^{25, 26} as well as on mammalian hearts consistently confirmed that a progressive rise in the perfusion pressure was associated with a progressive increase in the heart rate up to a certain critical level of pressure beyond which further increase in pressure either produced no change in the heart rate or the heart rate actually decreased. The average maximum rise in the heart rate when the

The surdo-cardiac syndrome

Three new cases of congenital deafness with syncopal attacks
and Q T prolongation in the electrocardiogram

Inga Jervell M D *

Rolf Fringslad M D **

Thor Oistein Enderby M D ***

Oslø Norway

In 1947 Jervell and Lange-Nilsen¹ described 4 siblings in whom deaf mutism was combined with a peculiar heart disease. The parents who were not related and two other children were healthy and had normal hearing. The deaf mute children who otherwise seemed to be quite healthy suffered attacks of fainting, these had occurred between the ages of 3 and 5 years. The attacks were often provoked by exercise or fear. Three of the children had died suddenly at the ages of 4, 7 and 9 years. One of the children is still alive at the age of 15 years.

Clinical and x-ray examinations which were performed in 3 of the children revealed no signs of heart disease.

However electrocardiograms from 3 of the children revealed a marked prolongation of the Q T interval. In one child a more extensive study showed a further prolongation of the Q T interval after exercise and quinidine medication where as a shortening was observed after atropine and particularly after digitalis. Changes also in the T waves were observed after effort and quinidine medication. Mechanic dysrhythmia evaluated by phonocardiography was not correspondingly lengthened.

None of the causes known to produce prolongation of the Q T interval could be

demonstrated. The blood levels of calcium, phosphorus and potassium were normal as were also the basal metabolic rate and the glucose tolerance test.

Autopsy was performed in one case but revealed no gross abnormality of the heart and the microscopic appearance of the heart muscle was normal.

The conclusion was that the unusual clinical symptoms, the exceptional electrocardiographic findings and the serious outcome of the illness represented a characteristic syndrome. The condition was supposed to be due to an inborn error of myocardial metabolism caused by some unknown enzymatic deficiency.

In 1958 Levine and Woodworth² described the case of an 8 year old deaf mute boy who from the age of 3 years had suffered attacks of fainting often provoked by fear or exertion. The ECG showed a long Q T interval with large and often bifurcated T waves. The clinical and x-ray examinations of the heart were normal and so also were studies of the electrolytes. The boy died suddenly at the age of 13 years. The heart appeared to be perfectly normal at postmortem examination.

In 1964 Fraser-Froggatt and James³ in an extensive publication described 9 cases

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(in 5 sibs) of the syndrome which they named the *cardio auditory syndrome*. The 9 patients ranged in age from 5 to 19 years and their first attack appeared at ages ranging from 1½ to 12 years. Three of the affected children were siblings in one family and 2 in another family. Three of the patients died suddenly at ages 3½, 3½ and 14 years. A hypochromic anemia was found in the majority of the patients and was suggested as an additional feature of the syndrome.

In addition to the aforementioned cases which presented a very typical syndrome 3 other cases are described without deafness but with an otherwise similar clinical and electrocardiographic picture.

In 1963 Romano, Gemme and Pongugliotti² described a 3 month-old female infant who had had periods of apnoeal attacks since the age of 2 months. The child had normal hearing and there was no evidence of deaf-mutism in the family. An ECG recorded during an attack showed ventricular fibrillation. Between the attacks the electrocardiogram revealed a marked prolongation of the Q-T interval and broad diphasic T waves. In addition ventricular extrasystoles with a very short coupling were registered. Two brothers with identical clinical symptoms had died at the ages of 44 days and 4 months.

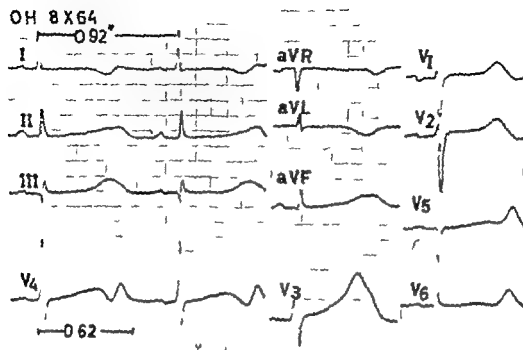
In 1964 Ward³ described a new familial cardiac syndrome in children. Two siblings, a girl and a boy, had had episodes of loss of consciousness from the ages of 16 and 15 months respectively. Both children had normal hearing. The boy died during an attack and the autopsy revealed no gross abnormality of the heart. Electrocardiograms at rest from both siblings showed an extreme prolongation of the Q-T interval. The ECG recorded during an attack showed ventricular fibrillation partly of the low voltage and partly of the high voltage type.

Examination of the relatives revealed that a 6-year-old brother and the father had quite normal electrocardiograms. The mother's ECG however showed a Q-T interval which was definitely prolonged as compared with normal values calculated from the usual formula. The mother had never had any clinical symptoms herself. There was however a history of sudden death in the mother's family.

Three additional cases of what we prefer to call the *sudden cardiac syndrome* are now reported. They demonstrate a typical clinical picture as well as electrocardiographic signs. Two of the children are girls, 13 and 10 years old, and the third is a 7-year-old boy. They had their first attacks at the ages of 9 and 2 years and 2½ months respectively. The children are not related.

Table 1 Clinical features of the published cases

Case	Author	Sex	Age at onset of faint	Age at death
1	Jervell and Lange-Nielsen 1957	M	1	9
2		F	5 yr	5
3		F	5	
4		F	3½	3
5	Romano, Gemme and Pongugliotti 1963	M	3 yr	1
6		F	1½ days	14
7		F	18 mo	
8		F	1½ yr	
9	Jervell, Thomsen and Føltoft 1966	F	18 m	
10		F	18 m	
11		M	1½	3½ yr
12		M	2½ yr	3 yr
13	Jervell, Thomsen and Føltoft 1966	F		
14		F	7 yr	
15		F	9 yr	
16		F	4 yr	
17		M	2½ m	



18. J. C. Lagarias, "On the number of representations of a number as a sum of four squares," *Journal of Number Theory*, vol. 9, pp. 167-180, 1977.

Table 1 presents some of the clinical features in these 3 cases and also in the earlier 14 published cases.

Case records

Case 1 Filed 08/11/92 In a Aug 20 1992 The parents
not shared th well in a long & ab-
long re he likes and h e norm l hearing there
e of deaf must as us the family She mother
bro an was repl s f presn nrs wh n men dr
e especially r suitable nd he had n t wear
any dev [he kls n was norm]

When the girl was 11, her mother discovered she was gay. She was very sad and she was very angry. She was very sad because she was gay and she was very angry because she was gay.

In July 1961, the day after she had the first attack, I saw my son when she had run about 200 meters to open gates in front of when she suddenly fell to the ground. His mother who was immediately at hand told her of this plan and seemingly did lose the tip were in fact of the eye. During the time a new lasted (about 7 minutes) she had a great deal of pain but he had been in constant of course. After the attack it had been about 10 days.

During the follow up 2 year he had 1 all of 7 attacks of unconscious. Last one was more or long lasting in the last. The attacks are provoked by exercise or by anger since September 1968 only 1 attack by anger in June 1973. This was provoked by anger and tension. She has the same

been in good health and has taken part in such exercises as swimming, skating, etc.

In connection with the first attack she underwent neurological examination and a EEG was recorded showing bilateral slow foci diagnostic of epilepsy. A suppurative process and the involvement of the parietal and frontal lobe was suggested in the differential diagnosis.

Since Oct 1964 she has been examined several times as the Medical Department Frondheim Central Ill put 111 general condition has been normal except for the deficiency Anemia which has looked in almost complete of vision and the final are consistent with the usual finding in retinal disease.

Cardiac output estimation is not reversible; any error of origin here means a wholly reliable measurement (Grade 3.2) is interpreted as being functional. As examination is within the use and configuration of the heart to be up to normal, the relative lumen 450 ml per square meter of body surface blood pressure is (60/60) mm Hg.

[illegible]

The I.C.C. value for examination on Oct 8 1961 was highly abnormal (Fig 1) The Q-T interval is markedly prolonged measuring 0.62 sec whereas the upper normal limit with R.R.d rate of 102 sec 0.40 sec (same formula) The T waves

927-1228 K02+012 ~ 014 m

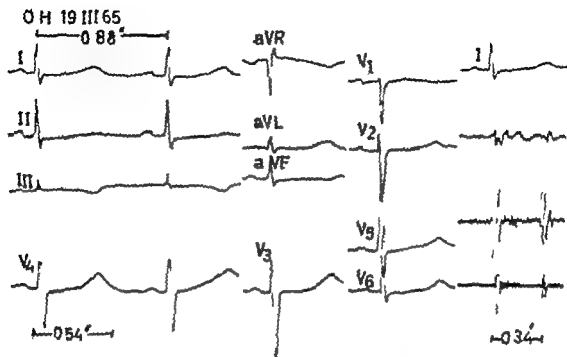


Fig. 3. Case 1. Oddly H. ECG recorded on March 19, 1965 after strenuous stair running immediately after the ECG in Fig. 2 was taken. R-R interval 0.88 sec. Q-T interval 0.54 sec (upper normal limit 0.40 sec). Mechanical systole 0.34 sec and the beginning of the second sound correspond to the middle of the T wave. Electrical systole is prolonged whereas mechanical systole has normal duration. A noteworthy feature is the fact that the ECG shows no ST depression in spite of full digitalization.

phalpic fremitus has been tried but without any result.

Treatment with digoxin was started on Feb. 2, 1965. She received 0.3 mg daily for 3 days then 0.05 mg daily for 1 week and later 0.1 and 0.05 mg on alternate days until March 2. Since then she has taken 0.1 mg of digoxin daily for shorter periods. The doses have had to be reduced because of nausea.

Since being placed on digoxin in March 1965 she has had only one attack which occurred once when she became frightened.

Since January 1965 she has been examined several times at the Medical Department, Tromsø Central Hospital. Except for a slight anorexia her general condition has been good. Audiometry showed in almost complete deafness identical to that usually recorded in cases of congenital deafness.

On examination of the heart it showed a loud systolic murmur (Grade 3) maximal in the third left intercostal space. The murmur was considered to be functional and related to the anemia. The heart size was normal and on x-ray study gave a heart volume of 370 ml per square meter of body surface. Blood pressure was 115/40 mm Hg.

The electrocardiogram, however, showed very marked abnormalities and with the same pattern as in Case 1. An ECG recorded on Jan. 9, 1965 (Fig. 4) showed a prolonged Q-T interval of 0.54 sec against the upper normal limit of 0.40 sec (1 jump formula). The T waves were also abnormal, neg-

ative in Leads I and aVL and huge with a bizarre shape in other leads, especially in Lead V₁. After exercise the ECG (Fig. 5) showed prolongation of the Q-T interval to 0.64 sec (upper normal limit 0.41 sec) and the shape of the T waves were also more abnormal. It was striking that the heart rate was not accelerated after exercise.

After the patient had been treated for 10 days with digoxin the ECG was slightly normalized and after 2 months on digoxin the ECG was almost normal (Fig. 6). The Q-T interval of 0.40 sec corresponded to the upper normal limit and the beginning of the second heart sound coincided with the end of the T wave. After exercise however the Q-T interval was again considerably prolonged in spite of a slower heart rate (Fig. 7). Mechanical systole on the other hand was shortened and the beginning of the second heart sound now coincided with the beginning of the T wave. In spite of digitalization to a degree that gave rise to no depression of the ST interval developed.

The laboratory data were as follows: Hb per liter = 3 mm Hg, hemoglobin = 10.7 Gm per 100 ml, HbC = 4.73 million per cubic millimeter, MCH = 21, Hematocrit = 40. Serum creatinine = 1.1 mgm per 100 ml, WBC = 5,800 per cubic millimeter. A blood smear showed slightly hypochromic RBC but with other normal forms.

Serum Cl = 107 mEq per liter, Serum Na = 140 mEq per liter, Serum K = 4.4 mEq per liter, Serum

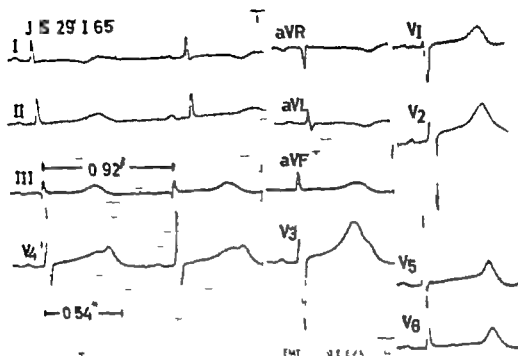
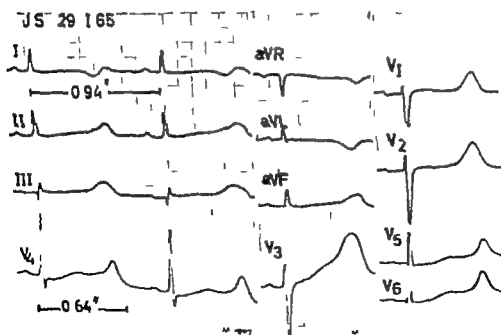


Fig 4 Case 2 Janna S ECG recorded on Jan 29 1965 P-P interval 0.92 sec Q-T interval 0.54 sec (upper normal heart 0.40 sec) Abnormal T wave in several leads



1. J. S. C. S. J. S. ECG taken Jan 29 1965 at 10:00 a.m. running, normal (by the ECG) 1.4 mV taken 1.1 sec 1.09 sec Q-T interval 1.0 sec (upper normal 1.1 sec) 0.41 sec) Mirrored exercise test at 1.1 sec 1.09 sec Q-T interval 1.1 sec 1.1 sec 1.1 sec

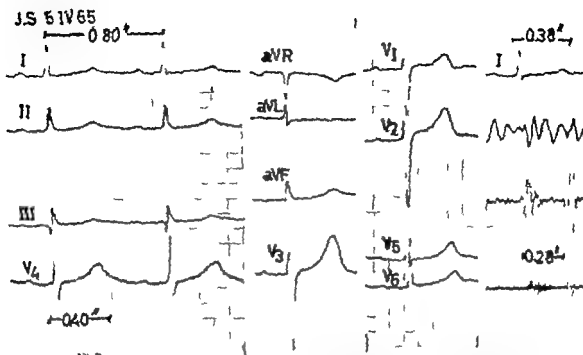


Fig. 2. (cont.) Normal ECG recorded on April 5, 1965 after digoxin medication for 2 months. The ECG was recorded at a heart rate of 108 per cent (upper normal limit 0.40 sec). Mechanical stroke 0.28 sec and the length of the second sound corresponds to end of the T wave. The normal electrical axis (I, II, III, aVR, aVL, aVF, V1, V2, V3, V4, V5, V6) is within normal limits.

C = 9.0 mg per 100 ml serum $\bar{S} = 4.0$ mg per 100 ml serum $\bar{M}_G = 2.7$ mg per liter $\bar{pH} = 7.41$ $\bar{H}_2\text{O}$ in m m RBC = 91 mg per liter. The urine was normal. Serum protein = 7.9 Gm per 100 ml. Electrolytes were normal except for the beta globulin which was slightly increased to 1.7 Gm per 100 ml (14.9 per cent). FBC and EKG were normal.

The laboratory data indicated a slight iron deficiency anemia and during treatment of the patient with iron the hemoglobin rapidly rose to normal levels.

Case 3. Feb 2, E. b. a Sept 5, 1937. The mother was 16 1/2 years old at the time of birth of this child. No information was available in regard to the father. The mother had attacks of epilepsy in adolescence. There was no case of deaf-mutism in her family.

When the boy was 2 years old it was realized that he was deaf. Apart from the deaf-mutism his development was satisfactory. At the age of 2 1/2 months he had his first attack of tonic contraction and unconsciousness. As he grew older he had similar attacks provoked by exercise (i.e. and anger generally) about 2 attacks per year. Since the age of 5 years he has experienced a second type of attack, usually triggered by exercise but occasionally by fear and anger. During these attacks he becomes very pale, claps his hands across his facial area, cries loudly, and turns very white. With uterine contraction, the mother was not able to see the child.

palpitations found to be regular and of normal frequency during these attacks. Repeated EEG examination has revealed no abnormality. Nevertheless, his condition was considered to be a form of epilepsy and he was treated with barbiturates and phenytoin without any noticeable effect.

Since May 1965 he has been examined regularly and controlled by the Children's Department. The child is normal. His general condition has been good except for his deaf-mutism. Audiometry has shown complete bilateral deafness. Maps of attack have been observed during his stay in the hospital.

Cardiological examination has not revealed any abnormal heart disease. The heart has been interpreted as being functional. The apical area of the heart was normal. The right ventricle was 220 ml per square meter of body surface. Blood pressure was 110/60 mm Hg.

Treatment with digoxin was started on May 21, 1965. After administration of digoxin was 0.14 mg of digoxin during the short period of observation after the fully developed attack. The child was considered to be in the normal range of the normal ECG.

An ECG recorded on May 15, 1965 was highly abnormal (Fig. 2). The Q-T interval was markedly prolonged to 0.40 sec, which is above the upper normal limit at R R of 0.38 sec. The upper limit of the normal range is 0.41 sec. (Fig. 2, normal range 0.38 to 0.41 sec.)

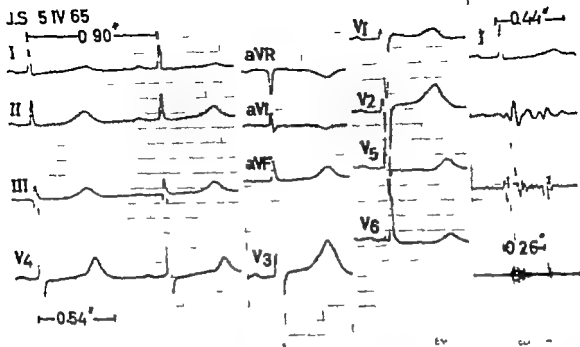


Fig. 7 Case 2 J. 12-lead ECG recorded on April 5, 1965 after cautious start running immediately after the ECG in Fig. 6 was taken. R-R interval 0.90 sec. Q-T interval 0.54 sec (upper normal limit 0.40 sec). Mechanical systole 0.26 sec and the beginning of the first sound corresponded to the beginning of the T wave. Electrical systole is prolonged after exercise whereas mechanical systole is shortened in spite of full digitalization. No obvious S-T depression has developed.

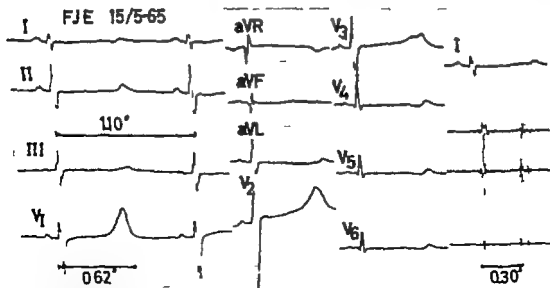


Fig. 8 Case 3 Fred J. ECG recorded on May 11, 1965. R-R interval 1.10 sec. Q-T interval 1.02 sec (upper normal limit 0.41 sec). Abnormal T waves in several leads. Mechanical systole normal. Distance from first to second heart sound is 0.30 sec.

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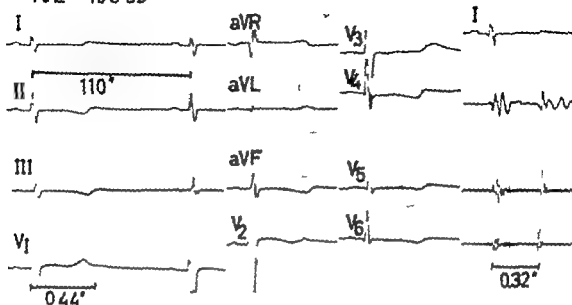


Fig. 4. Case 3. Fred J. E. ECG recorded on Aug. 11, 1963, after digitalis treatment for 3 months. The Q-T interval is normal. The PR interval is 110 sec. Q-T interval 0.44 sec. (upper normal limit 0.44 sec.) A black oval stroke normal and the long, noisy T of the first heart sound corresponds to the end of the T wave.

grams per liter. The hemoglobin value was normal (10.0 g/l) and the hematocrit value was normal (30.7%). After digitalis medication was started the ECG in the lead aVR showed the Q-T interval 0.44 sec, just corresponding to the upper normal limit (Fig. 4, Form 1). The boy was at that time fully healthy and without symptoms of asthma.

The following laboratory data were obtained in May 1964: ESR per hour = 4 mm. WBC = 5,500 per cubic millimeter. Hemoglobin = 10.5 Gm per 100 ml. RBC = 5.8 million per cubic millimeter. MCH = 18.

Serum Cl = 110 mEq per liter. Serum Na = 142 mEq per liter. Serum K = 4.8 mEq per liter. Serum Ca = 9.4 mg per 100 ml. Serum P = 5.2 mg per 100 ml. Serum Mg = 3.2 mEq per liter. Potassium in RBC = 10.1 mEq per liter. Cholesterol = 200 mg per 100 ml. BUN = 5 gamma per 100 ml. Serum protein = normal amount, but gamma-globulin reduced to 5 per cent. Immunoelectrophoresis showed hypogammaglobulinemia equally distributed in all three fractions. The serum fatty acids were normal in amounts and distribution. Chromatography of amino acids and sugars in the urine showed normal values. EKG and EEG were normal. Chromosome examination did not show any abnormalities.

The bronchial asthma symptoms responded rapidly to steroid treatment.

Discussion

The attacks Fraser and associates⁴ have given a very thorough description of the

attacks in patients with the pseudo-myocardial infarction syndrome. They describe three categories of attacks: viz. episodes without loss of consciousness; those with loss of consciousness and recovery; and those terminating fatally.

Attacks without loss of consciousness occurred in Fraser and Lange-Nielsen's Case 3, in Levine and Woodworth's case in Fraser and associates' Cases 1, 4, and 5, and in our Case 3. Possibly such minor attacks may have occurred undetected in other cases. A common feature of these attacks is that the children stop moving, lie down or sit down, and refuse to go further. They grasp their breast or stomach and moan or cry. The pulse is normal during the attacks. After some minutes the attack will be over and the patient will again feel well. The attacks are also provoked by exertion or mental stress. The resemblance to attacks of angina pectoris is obvious. These attacks however are certainly not caused by coronary ischemia. The metabolic disturbance may, however, on special occasions, for example after exercise, result in an accumulation of metabolites.

Concerning the attacks with loss of con-

sciousness and eventually death the mechanism is obviously a different one but cannot be determined with certainty until an ECG during such an attack is available. The attacks have however the character of Adams Stokes attacks and are probably caused by ventricular fibrillation.

The electrocardiographic findings. The electrocardiographic abnormalities in the three cases described show a striking resemblance to one another as they do all to the findings in the previously published cases. Typical is a marked prolongation of the Q-T interval. The QRS complexes however are of normal appearance and duration. The prolongation of the ventricular complex is therefore entirely due to prolongation of the ST interval and T wave. A disorder of repolarization corresponding to Phases 2 and 3 must therefore be the underlying cause.

As previously observed⁴ the appearance of the ECG may change from day to day. This is probably explained by the fact that different factors may influence the ECG in these cases. It has been shown previously that exercise and guanidine medication prolong the Q-T interval whereas atropine and digitalis medication have a shortening influence.

In the cases reported here the effect of cautious exercise on the ECG is convincingly demonstrated (Figs 3, 5 and 7). In some instances prolongation of the Q-T interval after exercise appeared without any change in the heart rate (Fig. 5).

After digoxin medication on the other hand the Q-T interval decreased to just below the upper normal limit (Figs 2, 6 and 9). Furthermore it is remarkable that digitalization to an extent which provoked clinical signs of intoxication did not produce ST depression.

A further characteristic finding is that mechanical systole, evaluated by the distance between the first and the second heart sounds, is of normal duration in contrast to electrical systole (Figs 3, 7 and 9).

The electrocardiograms also show marked abnormalities of the T waves which are partly negative, partly bifurcated, diphasic or broad and low. The T waves also vary in appearance from one examination to another and become more abnormal after exercise whereas they normalize after digi-

toxin medication. Remarkable also is the fact that neither extrasystoles nor other arrhythmias have ever appeared in the numerous electrocardiograms recorded in our patients.

The abnormalities in the electrocardiogram resemble those due to hypokalemia but neither in our 3 cases nor in any of the previously published cases has hypokalemia ever been found and the potassium content in red blood cells was also normal. Nor have any other electrolyte disturbances been recorded. Therefore a biochemical explanation for the ECG abnormalities cannot be given. Possibly the membrane permeability for electrolytes is affected due to some inborn enzymatic deficiency.

Postmortem findings. Autopsy has been performed in 5 cases. In 3 of them (Jervell and Lange-Nielsen's Case 1, Levine and Woodworth's case and Fraser and associates Case 6) there were no convincing pathologic findings on microscopic and macroscopic examination. In Fraser and associates Cases 1 and 7 the autopsies were conducted with special reference to the conducting system and they showed consistent abnormalities, some compatible with sudden death. For details we refer to their original communication³ (pp. 376-377 and 379). Possibly some of their pathologic findings may have been caused by anoxemia during the Adams-Stokes attacks.

Genetic problems. Fraser, Froggatt and Murphy⁴ have discussed the genetic problems of the syrd cardiac syndrome. They find a high frequency of consanguineous unions among the parents of affected children and they conclude that the data are consistent with a hypothesis of recessive inheritance. Those heterozygotes for the gene may have slight or moderate prolongation of the Q-T interval. The syndrome accounts for a small proportion (<1 per cent) of the total number of children with severe educational deafness in the British Isles.

In our Cases 1 and 2 there was no consanguinity among the parents. In Case 3 the father is not known. In all 3 cases we have examined the relatives and in Cases 1 and 2 the clinical and ECG findings were normal in parents as well as in siblings.

Concerning Case 3 the mother has a history of attacks of syncope in girlhood but

no details are known. She has however no signs of organic heart disease. Her ECG shows a slight prolongation of the Q-T interval (with a R-R distance of 1.00 sec the Q-T intervals are 0.42 to 0.44 sec against an upper normal limit of 0.42 sec). There is however no discrepancy between mechanical and electrical systole. After exercise the R-R interval shortened to 0.38 sec and the Q-T interval to 0.36 sec against an upper normal limit of 0.33 sec. This means a relative prolongation of the Q-T interval after exercise. However the relationship between mechanical and electrical systole is normal also after exercise.

We must conclude that our cases do not give any positive information about heredity of the surdo cardiac syndrome.

Relationship between abnormal myocardial repolarization and deafness. Bruser and associates⁴ have discussed this problem in detail and they conclude as follows: It is suggested that the association of congenital deafness with retinitis pigmentosa (Lsher's syndrome) with a defect in thyroxine synthesis (Pendred's syndrome) and with a defect in cardiac conduction (a third distinct syndrome) may reflect pleiotropic manifestations of three widely disparate chromosomal errors of metabolism. The common feature of congenital deafness may be associated with the extreme sensitivity of the VIIIth nerve to metabolic disturbances and chemical toxins. To this we have nothing to add but the problem is of importance for the discussion about the relationship between the surdo cardiac syndrome and the syndrome described by Romano and associates and by Ward.

Relationship between the surdo cardiac syndrome the syndrome described by Romano and associates and by Ward and attacks in children of ventricular fibrillation without Q-T prolongation. The surdo cardiac syndrome and the syndrome described by Romano and associates and by Ward have in common the appearance of episodes of unconsciousness, also sudden death in some cases and furthermore prolongation of Q-T in the ECG. But in important difference is the complete congenital deafness which is not found in the cases described by Romano and associates and by Ward. In these latter cases the symptoms also start at a very early age viz. 2, 16 and 17

months but children with the surdo cardiac syndrome have their first attacks later the majority of them at an age between 3 and 7 years.

It is also worth mentioning that several cases of Adams Stokes attacks caused by ventricular fibrillation have been described in children without organic heart disease and with a normal Q-T interval in the ECG.¹⁰

Thus three syndromes may be distinguished in children with Adams Stokes attacks but without signs of organic heart disease: (1) the surdo cardiac syndrome, (2) the syndrome with prolonged Q-T interval and attacks of ventricular fibrillation but without deafness and (3) the syndrome with multiple extrasystoles and attacks of ventricular fibrillation but without deafness and without prolongation of the Q-T interval in the ECG.

Diagnosis, treatment and prognosis. No diagnostic problem will exist if all physicians who care for deaf mute children are familiar with the syndrome. An ECG will immediately make the diagnosis clear. In many cases as occurred in our 3 cases the attacks have been mistaken for epileptic fits and the patients have for a shorter or longer time been given antiepileptic treatment.

Taking into consideration also the other syndromes mentioned we recommend that an ECG be registered in all children with a history of fits or attacks of fainting or unconsciousness and preferably that an ECG be recorded after exercise also.

The importance of a correct diagnosis is evident because adequate treatment may possibly be life saving and the patient can be spared ineffective antiepileptic treatment. A correct diagnosis will also be important for prognostic considerations.

In regard to treatment the following facts are of significance: (1) Because the attacks are usually provoked by exercise, fright, anger etc. the children in as far as possible must be kept away from physical as well as mental stress. (2) Digitalis in adequate doses seems to be indicated. The normalizing effect on the ECG is of course shown in Jervell and Lange-Nielsen Case 1 and in our 3 cases. In our Case 2 the treatment also had a convincingly favorable effect on the attacks. (3) The symp-

1/10/7
10/10/7

toms seem to lessen as the children get older and complete recovery may be a possibility. This question may be settled by further observation of the affected children.

The prognosis is undoubtedly very grave. Seventeen patients with the surdo-cardiac syndrome have so far been described and 7 of them have died at ages from 3 to 14 years. However the prognosis may be considerably improved through a closer supervision of the children together with adequate digitalization.

Conclusion and summary

Three cases of the surdo-cardiac syndrome are described. Since the first publication in 1957 17 cases are now known. The symptoms and signs are very characteristic; the following are the most important. There is congenital deafness with attacks of unconsciousness, probably Adams-Stokes attacks caused by ventricular fibrillation or milder attacks resembling angina pectoris. The attacks are usually provoked by exercise or mental stress such as fear and anger.

In the ECG a marked prolongation of the Q-T interval is found with abnormal and bizarre T waves. The ECG abnormalities increase considerably after exercise. In contrast mechanical systole is quite normal and shortens after exercise. Digitalization has a very distinct normalizing effect on the ECG. At least in one case (our Case 2) digitalization also had a beneficial influence on the attacks of unconsciousness.

The cause of the abnormal repolarization phase in the myocardium is supposed to be due to an inborn error of metabolism caused by some enzymatic deficiency which may possibly hamper the transport of electrolytes through the cell membrane.

A similar syndrome with Q-T prolongation and attacks of ventricular fibrillation is described by Romano and associates and by Ward. This syndrome however differs from the surdo-cardiac syndrome in the absence of congenital deafness. From a clinical point of view it seems to be better not to confuse the two syndromes.

Addendum

Case 3 Fred J. E. born Sept. 7, 197

This patient was re-examined on April 30, 1966 after he had taken acetyldigoxin 1.14 mg daily for 11 months. Since October 1965 he has had no attacks of unconsciousness and also he has tolerated physical exercise much better. A further normalization of the ECG was found with a Q-T interval of 0.33 sec. however this was again prolonged to 0.44 sec after exercise starting running for 1 minute. The exertion obviously induced pains in his chest since he clasped his hands across his chest and cried. The pains subsided after about 1 minute. In this case as well as in Case 2 digoxin apparently has had a favorable effect not only on the appearance of the ECG but also on the attacks of unconsciousness and on the patient's ability to tolerate physical exercise.

We are greatly indebted to Dr. Terje B. Øster, chief physician at the Home for the Deaf, Norway and to Dr. Erling Esp. Øst, MD at the School for Deaf Children in Trondheim for their valuable help.

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A comparison of the hemodynamic effects of tachycardia produced by atrial pacing and atropine

Bernard D Kosowsky MD*

Emanuel Stein MD

Sun H Lau MD

John W Lister MD

Jacob I Haft MD

Anthony V Dumala MD

Staten Island NY

Atropine has been used to produce increases in heart rate both clinically and in investigations relating the effects of heart rate to cardiac function. The chronotropic effect of atropine is well established. However, it has not been clearly determined whether atropine affects other cardiovascular parameters. Comparisons between the control and atropine states are difficult to evaluate because it is not clear whether the changes in hemodynamics that may occur are secondary to tachycardia or are manifestations of the vasodilator or direct effects of the drug.

With the use of atrial pacing it is possible to increase the heart rate without significantly altering the hemodynamic state.¹ It is possible therefore to study the effects of atropine independently of its chronotropic property by comparing values obtained with atropine to those in the resting state at similar heart rates. The present

investigation was designed to compare the hemodynamic effects of tachycardia produced by atrial pacing and by atropine in normal subjects.

Methods

Investigations were performed in 9 normal male volunteers 23 to 30 years of age during cardiac catheterization. All studies were carried out with the subjects in the supine position in a resting, nonmedicated postabsorptive state.

Through an intercostal vein a No 7 or 8 Courmand catheter was positioned in the main pulmonary artery and a No 5 tripolar electrode catheter was positioned along the lateral wall of the right atrium. A No 18 Courmand needle was inserted into a brachial artery. Pressures were obtained by means of Statham 231D strain gauges. Cardiac outputs were determined in duplicate by the dye-dilution technique.

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with 7.5 mg. of indocyanine green dye being injected into the pulmonary artery and with blood sampled from the brachial artery through a cuvette densitometer. All recordings were made on an eight channel photographic oscilloscopic recorder. Cardiac outputs were calculated from the inscribed curves using the Stewart-Hamilton formula.

Atrial pacing was accomplished by means of a battery powered pacer connected to the electrode catheter. The atria were paced at various rates up to 160 beats per minute or until A-V block occurred at a milliamperage of approximately twice threshold. The pacer was not turned off during the intervals between determinations.

Mean arterial pressures and mean aortic pressures were planimetrically determined over two respiratory cycles. The systolic ejection time (SET) was derived from the brachial arterial pressure pulse. The tension time index (TTI) was calculated according to the method of Sarnoff and associates.⁷ Stroke index (SI), total peripheral resistance (TPR), mean systolic ejection rate (MSER) and left ventricular work index (LWI) were calculated from the standard formulas.

In each subject cardiac outputs, electrocardiograms and arterial pressure tracings were recorded at sinus rhythm and after 3 to 5 minutes of atrial pacing at various heart rates. These studies were repeated 3 minutes after the intravenous injection of 2 mg. of atropine sulfate administered over a 1 minute period.

Results

The data from all of the subjects are presented in Table 1. Statistical analyses were made on pairs of values in individual subjects obtained at similar heart rates (within 10 beats per minute) in the control and atropine states. These values are noted by an asterisk in Table 1.

Cardiac index. The administration of atropine resulted in no significant change in cardiac index ($p > .90$) (Fig. 1). Increasing the heart rate by means of atrial pacing did not significantly change the cardiac index although there appeared to be a slight decrease in cardiac index at the maximum heart rates obtained with and

without atropine. The stroke index varied inversely with heart rate and was not affected by atropine at similar heart rates.

Brachial arterial pressure. The brachial arterial pressure, mean arterial pressure and the mean systolic pressure were unchanged by atropine ($p > .50$) or by changes in heart rate.

Systolic ejection time. At similar heart rates there was no significant difference between the SET obtained by atropine and that obtained by atrial pacing ($p > .90$) (Fig. 2). Increases in heart rate by atrial pacing resulted in a linear increase in SET with and without atropine.

Tension time index. There was no significant difference between the TTI before and that after the administration of atropine at similar heart rates ($p > .30$) (Fig. 3). The TTI increased with heart rate paralleling the changes in SET.

Total peripheral resistance. The TPR was not significantly altered by the administration of atropine ($p > .60$) or by changes in heart rate.

Mean systolic ejection rate. At similar heart rates the MSER before and that after the administration of atropine were not significantly different ($p > .50$). Under both conditions the MSER varied inversely with heart rate.

Left ventricular work index. The LWI was not altered by atropine ($p > .90$) or by changes in heart rate.

Discussion

The effect of atropine on cardiac output has been extensively investigated. Several studies have shown an increase in output after intravenous atropine,⁴ although other studies in human beings and dogs failed to show any changes.^{1,2,10} Lancaster and his associates¹ have shown that atropine and rapid atrial pacing both have an immediate effect of increasing cardiac output with a return to control values after a few minutes. In the present study since the pacer was not turned off between determinations the effects of acutely changing the heart rate were not evident.

Because of the previous unavailability of similar heart rates without atropine comparisons of other parameters that might be affected by atropine have not

Table 1—Cont'd

Patient age (y)	HR (per min)	CI (L/min/M ²)	SI (ml/M ²)	BI (mm Hg)	SET (sec/min)	TTI (mm Hg sec/min)	TIR (dynes/cm ² M ²)	MSER (ml/sec/M ²)	LVFI (Lg M/min M ²)
WM	0	3.58	51	108	23	2.880	2.470	158	5.78
45	100	4.10	41	110	26	3.000	2.140	158	6.18
	120	4.10	34	108	30	3.350	2.110	136	6.05
	140	3.54	25	110	31	3.560	2.490	114	5.35
	110A	4.39	40	107	28	3.050	1.950	157	6.50
	120A	3.88	32	110	30	3.700	2.260	129	5.83
	140A	4.37	31	103	31	3.250	1.890	140	6.15
	160A	3.89	24	98	35	3.460	2.010	111	5.15
WC	87	3.44	42	101	25	2.610	2.370	137	4.74
57	100	3.79	38	100	26	2.700	1.10	145	5.17
	125	3.80	30	107	30	3.700	2.140	129	5.30
	137	3.87	28	104	37	3.580	2.180	118	5.30
	150	3.55	24	99	33	3.520	2.740	108	4.80
	130A	3.79	28	103	30	3.240	2.160	123	5.70
	151A	3.64	27	101	31	3.440	2.200	118	5.01
	148A	3.26	27	107	37	3.570	2.550	10	4.7
CI	100	5.76	53	107	27	3.070	1.640	194	7.7
44	110	5.28	48	107	29	3.180	1.640	187	7.8
	130	4.72	36	107	3	3.060	1.830	149	7.00
	150	5.78	35	98	34	3.400	1.500	157	6.5
	144A	5.47	41	95	31	3.350	1.410	178	7.00
	138A	5.39	39	95	31	3.410	1.470	14	6.95

generally been made. In a study of the effect of atropine on coronary blood flow, Corin⁷ found that myocardial oxygen consumption per systolic second was unchanged by atropine thus implying that the effect of atropine was solely related to its chronotropic property.

Atrial pacing provides a safe and effective means of producing increased heart rates. The impulses from the atrium are conducted through the A-V node and depolarize the ventricles in a normal fashion⁸ thus simulating sinus rhythm. Ross and associates¹ and Stein and co-workers⁹ have shown that alterations in heart rate within the physiologic range produce no change in the hemodynamic state. It is possible therefore to compare cardiac dynamics at similar heart rates obtained by atrial pacing and by atropine to determine whether atropine has any effects other than those related to its chronotropic property.

In the present study we found that the changes in cardiac dynamics produced by a dose of atropine sufficient to completely eliminate parasympathetic activity¹ were limited to those parameters which are directly influenced by changes in heart rate i.e. SET, TTI, SI, and MSER. Those parameters which have been shown to be independent of heart rate i.e. CI, LVFI, and TIR remained unchanged. Braunwald and associates¹ have described the effect of sympathomimetic amines on shortening of the SET. Since the systolic ejection times at comparable heart rates before and after atropine are almost identical one can infer that there is no unmasking of sympathetic activity and that therefore there is no parasympathetic tone acting to control this parameter under normal conditions. Atropine resulted in no change in TTI at comparable heart rates. In so far as the TTI reflects myocardial oxygen consumption this confirms

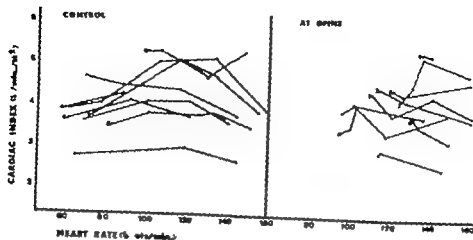


Fig 1 Comparison of cardiac index at various heart rates before and after the intravenous administration of 1 mg of atropine sulfate.

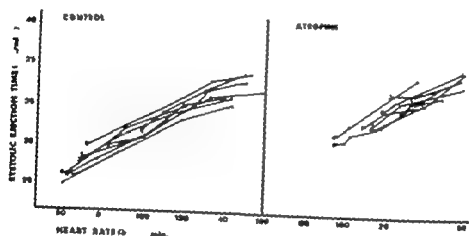


Fig 2 Comparison of systolic ejection time at various heart rates before and after the intravenous administration of 1 mg of atropine sulfate.

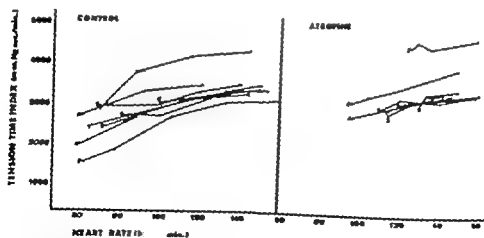


Fig 3 Comparison of the tension time index at various heart rates before and after the intravenous administration of 1 mg of atropine sulfate.

Gorlin's findings. The MISER has been used to describe left ventricular function because it is believed to reflect the velocity of muscle shortening.¹⁴ Its validity has been questioned under conditions in which the ventricular volume is changed¹ and therefore comparisons of MISER at different heart rates cannot be evaluated. In this study the MISER was unchanged by atropine at similar heart rates and stroke volumes. On the assumption that no significant change in ventricular volume occurred this implies that atropine has no effect on left ventricular function.

In conclusion the major effect of parasympathetic blockade with atropine in normal human beings is an increase in heart rate. Any alterations in the parameters that were studied can be accounted for on the basis of change in heart rate alone. Although the effects of vagolytic intervention on atrial function have not yet been studied it is apparent that blockade of parasympathetic tone in normal subjects has no significant effect on cardiovascular hemodynamics.

Summary

Cardiac outputs and arterial pressures were obtained in 9 normal subjects in whom various degrees of tachycardia were induced by atrial pacing before and after the intravenous administration of 2 mg of atropine. At similar heart rates atropine produced no change in cardiac index, stroke index, brachial arterial pressure, systolic ejection time, tension time index, total peripheral resistance, mean systolic ejection rate or left ventricular work index. It is apparent that the effects of atropine on cardiovascular hemodynamics are limited to those related to its chronotropic effect.

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Superiorly oriented electrocardiographic axis in infants with the rubella syndrome

Elizabeth H. Halloran M.D.
Shyamal K. Sanjay M.B.B.S.**
Thomas H. Gardner M.D.
New Haven Conn.*

Left axis deviation or a rightward superiorly oriented mean electrical axis in the electrocardiogram is rare in infants and when present is usually associated with specific cardiac anomalies such as the endocardial cushion defect. Since this electrical axis was observed in 12 of a series of 23 infants with congenital heart disease associated with the rubella syndrome it is being reported as an unusual observation with some speculation as to possible causes.

Clinical data (Table 1)

Following the rubella epidemic in the spring of 1964, 23 infants with congenital heart disease whose mothers had a history of rubella were observed at the Yale New Haven Medical Center. Rubella virus was isolated from a throat swab culture in 21. Although multiple organ systems were involved, only the cardiac anomalies will be discussed. Cardiac catheterization was performed in 13 infants. A large left to-right shunt ($QP/QS > 2$) through a patent ductus arteriosus was demonstrated in 9, 3 of whom had additional peripheral

pulmonic stenosis. A left to right atrial shunt was observed in 4 of these infants, possibly through a dilated foramen ovale secondary to the large ductal shunt rather than representing a true atrial septal defect. A small to moderate sized patent ductus ($QP/QS < 2$) was demonstrated in 4, 3 of whom had peripheral pulmonic stenosis. One of these also had a left to right atrial shunt and another had probable pulmonic valvular stenosis.

The clinical diagnoses in those infants who were not catheterized are tabulated in Table 1. Five are considered to have a patent ductus arteriosus, 4 a peripheral pulmonic stenosis and 1 a tetralogy of Fallot.

Eight infants underwent surgery with division of the patent ductus.

Electrocardiographic and vectorcardiographic data

Method. Twelve lead electrocardiograms were obtained with a Sinfar-Poly Beam or direct writing recorder and vector cardiograms were obtained with a Sinfar-Poly Beam recorder using the Frank

* Dr. Halloran was formerly at Yale University School of Medicine, Department of Pediatrics, New Haven, Conn.
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Address: Department of Pediatrics, Yale School of Medicine, 333 Cedar Street, New Haven, Conn. 06510.
Present address: Department of Pediatrics, Research Foundation, St. Peter's Hospital, New Haven, Conn. 06511.

Table I. Clinical data

Sex	Case	Site	1 sec solution	Catheterization	Surgery	Diagnosis
Superior	1 SD	M	+	+	+	PDA
	2 I Z	M	+	+	+	PDA
	3 R W	F	+	+	+	IDA
	4 R W	F	+	+	+	IDA
	5 J B	M	+	+	+	IDA Peripheral IS
	6 S C	F	+	+	-	IDA Peripheral PS
	7 W M	M	+	+	-	PDA
	8 J V	M	+	+	-	IDA Valv. S Peripheral PS
	9 W V	M	+	+	+	IDA
	10 F S	F	+	-	-	IDA
	11 J M	M	+	-	-	IDA Peripheral IS
	12 M F	M	+	-	-	Peripheral IS
Normal	13 J G	F	+	+	+	IDA
	14 D D	F	+	-	-	PDA
	15 R V	F	+	+	+	PDA Peripheral IS
	16 J L	F	+	-	-	PDA
	17 P M	F	-	-	-	Peripheral IS
	18 J K	M	+	-	-	Peripheral PS
Right	19 S G	F	+	+	-	PDA Peripheral IS
	20 M A	F	+	-	-	IDA
	21 C A	M	-	-	-	Peripheral IS
	22 V S	F	+	+	-	PDA Peripheral IS
	23 V C	F	+	-	-	Tetralogy

PDA: Patent ductus arteriosus; PS: Pulmonary stenosis.

lead system. Records were obtained during the first 2 months of life in 16 infants in 8 during the first week of life. Frontal vector rotation and direction were derived from simultaneously inscribed leads according to the method of Crant¹ when vectorcardiograms were not directly recorded. The mean electrical axis was estimated to the nearest 5 degrees and defined according to the criteria of the New York Heart Association. Interpretation of ventricular enlargement was based on the criteria of Keith and associates.²

Results (Table II)

RYTHM. A normal sinus rhythm was present in all. One infant had premature ventricular contractions at the age of 3 months that did not persist. The Wolff-Parkinson-White syndrome, Type II, was observed in 1 infant at 2 weeks of age and has persisted to the present.

Q WAVES. Tall peaked I waves were observed in Lead II in 4 infants with a

patent ductus. One infant with a large ductus had electrocardiographic evidence of left atrial enlargement with a deeply negative I wave in Lead V₁.

P-R AND QRS INTERVALS. The duration of the P-R and QRS intervals were normal except in the case of the Wolff-Parkinson-White syndrome.

ELECTRICAL AXIS. A superior or leftward oriented mean electrical axis was observed in 12 infants ranging from -160 to 0 degrees. Before 2 months of age the majority were in the -90 to -140 degree quadrant (Fig. 1A). After 2 months a shift in axis was noted in 7. In 3 the axis shifted from the superior right quadrant to the left and in 2 it shifted to a normal or a right orientation (Fig. 1B). In the infant with our superior orientation the axis was variable but none showed an extreme rightward deviation. In no case was there a shift from a normal to a superior axis. After division of the ductus the superior

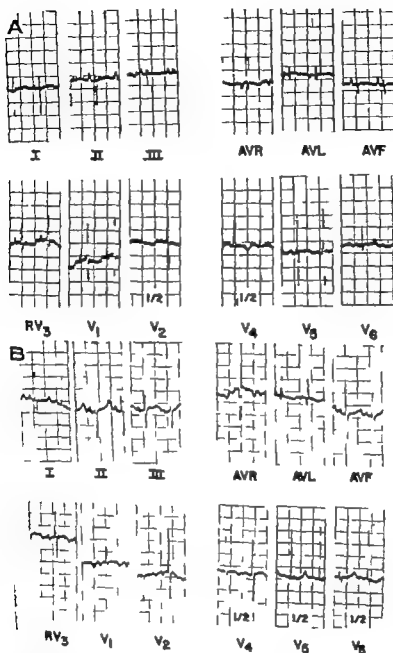


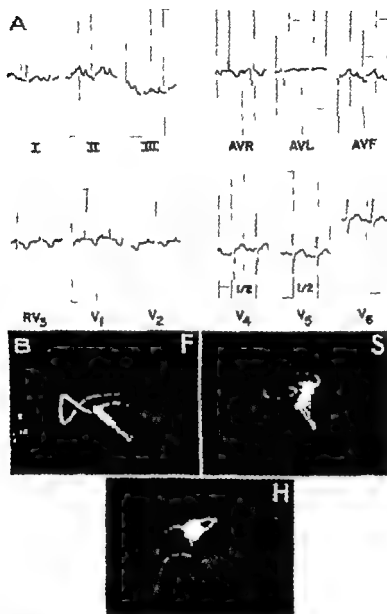
Fig. 2 Case 10 P.S. A Age 4 days. Electrocardiogram shows a normal right ventricular preponderance in this newborn infant with a large patent ductus. B Age 4 months. There is a shift in axis to 0 degree with evidence of left ventricular hypertrophy.

orientation persisted when it was present preoperatively.

VENTRICULAR HYPERTROPHY. In those infants with a superiorly oriented axis the precordial leads were indicative of right ventricular hypertrophy in 4 combined ventricular hypertrophy in 3 and appeared to be normal in 4 (Fig. 2). In

those infants with a normal or a right axis there was right ventricular hypertrophy in 3 combined ventricular hypertrophy in 3 and left ventricular hypertrophy in 1 and 4 appeared to be normal.

VECTORCARDIOGRAMS. In those infants with a superiorly oriented axis the frontal vectors were variable. Rotation of the

[illegible]

frontal vectors was clockwise in 3, counter clockwise in 3, and figure of eight in 5. After 3 months of use the rotation was counterclockwise or figure of eight in all but 1 (Fig. 3). The frontal vector showed one of four patterns (Fig. 4) and was oriented along the horizontal axis. There was a generally narrow loop even when the mean electrical axis in the electrocardio-

from was calculated to be in the range of -90 degrees.

Discussion

The unusually high incidence of a supranormally oriented axis prompted a review of the data for possible correlation with cardiac diagnosis or ventricular hypertrophy. Although a clockwise extreme

deviation is present it is the result of a conduction disturbance in particular in the anterior division of the left main bundle branch.⁹ Myocardial fibrosis has frequently been implicated.^{10,11} Left axis deviation has been produced experimentally in the guinea heart by interruption of the anterior ramus of the left bundle branch.¹ The well known association of left axis deviation with the endocardial cushion group of anomalies has been related to an anomaly of the left bundle branch system.¹ A recent review correlating a dominant S₁S₂S₃ pattern in children with congenital heart disease included 2 cases of patent ductus arteriosus¹ but it was considered that this pattern usually signifies right ventricular hypertrophy. In our series the 2 patients who retained an axis in this quadrant after the age of 2 months did have right ventricular hypertrophy.

The extensive studies which were carried out after the rubella epidemic in 1964 have led to the concept of an active disseminated infection in affected infants involving multiple organ systems. Virus can be cultured for some months after birth even in the presence of antibody in the newborn host and has been cultured from various organs at necropsy.¹ The pathological demonstration of myocardial necrosis and vascular degeneration in 2 infants with electrocardiographic evidence of severe myocardial damage suggests that active myocarditis may be present in some infants and it is conceivable that the conduction system could be affected.¹² The general lack of correlation with ventricular hypertrophy or with the hemodynamic situation leads to the speculation therefore that this unusual superior orientation may reflect an abnormality of depolarization possibly directly related to the rubella syndrome which may be temporary or permanent.

Summary

An unusual superiorly oriented mean electrical axis has been described in 12 of a series of 23 infants with congenital heart disease associated with the rubella syndrome. The majority of infants had a patent ductus arteriosus or peripheral pulmonary stenosis. The electrical axis did not correlate with the anatomic diagnosis

of ventricular hypertrophy and the possibility that this axis may represent a conduction disturbance is discussed.

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Unusual features of pheochromocytoma

An experience with 10 patients

N O Atak MD

J L Camp III MD

J J Tinsley MD

4 B Meica MD

Charlottesville Va

The correctness of the hypertension caused by pheochromocytomas makes their diagnosis and removal of the utmost importance. These tumors remain difficult at times to diagnose despite an ample literature on their clinical manifestations.¹⁻⁵ Their small size, inaccessible location and frequently atypical clinical presentation contribute largely to this problem. This paper describes some atypical aspects of pheochromocytomas in an experience with 10 patients. The clinical features of these patients are summarized in Table I. The 24 hour urinary excretions of catecholamines, 3 hydroxy-4 methoxy mandelic acid (VMA) and 17 ketosteroids in some of these patients are listed in Table II.

Methods

Urinary catecholamines were measured in the fluorometric method of von Euler and Heding.⁷ No correction was made for recovery rate which proved to be 72 to 35 per cent. Plasma levels of catecholamines were quantitated in the method of Aronow and Howard.⁸ VMA excretion was measured by the method of Sunderman and co-workers⁹ and 17 ketosteroids by a modification¹⁰ of the method described by Metcalf.¹¹ Total catecholamines were

expressed as a percentage of their upper limits of normal which was calculated as follows:

$$\frac{\text{Total catecholamines} - (\text{Norepinephrine} + \text{Epinephrine})}{10} \times 100 = \%$$

One hundred per cent is the upper limit of normal for total catecholamines by this expression. The reason for this is to give proportionate significance to both VLE and F values whose upper limits of normal excretion differ threefold. This is discussed elsewhere.¹²

Case reports

Case 1—A 50-year-old white woman noticed increasing nervousness, facial flushing and menstrual irregularities during the year prior to admission. She also experienced breast tenderness, erythema, perspiration and palpitation. She developed intermittent paroxysmal tachycardia with before admission 11 per cent thyroidism was suspected but is kept below 100 per cent for a basal metabolic rate of 100 per cent. Her serum protein bound iodine is 4.5 mg per cent.

She had sustained hypotension of 13/100 mm Hg and a tachycardia of 140 per minute. She was febrile, blood sugar elevated, but not ill. Her fecal flora, blood, sputum, excretions were all negative. She performed a physical examination of the gastrointestinal tract, heart, lungs and was in the green heart stage.

Her operation date started pathologic and she was no candidate for surgery when her catecholamine

From the Department of Endocrinology and Metabolism, University of Virginia School of Medicine, Charlottesville, Virginia.

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Table I Clinical feature of 10 patient with proved pheochromocytoma

Patient	Age sex	Years with symptom	Excessive sweating	Headache	Anxiety	Flush	Paroxysmal hypertension
1	50 F	1	+	III	+	+	0
2	4 F	2	0	+	+	II	0
3	15 F	1	+	—	+	+	+
4	40 M	15	II	+	0	0	+
5	57 M	?	+	+	0	0	+
6	47 F	1	+	+	+	0	+
7	30 F	?	+	+	0	0	0
8	18 F	3	+	+	0	III	+
9	21 F	1 mo	0	+	0	0	+
10	58 F	4	+	+	0	+	+

VE (ml) per hour total VE (ml) per hour E (mg/24 h) Total catecholamines (%) I VI I 17 Adrenosteroids (mg/24 h)

Table II Twenty four hour excretion of VE, E and total catecholamines by 7 patients with proved pheochromocytoma and of 17 ketosteroids and I VI by some of these patients

Patient	VE (mg/24 h)	E (mg/24 h)	Total catecholamines (%)	I VI I (mg/24 h)	17 Adrenosteroids (mg/24 h)
1	9.6	180	493.2	—	1.4
2	6.0	451	1086.6	—	25.8
3	130	620	1098.3	—	—
4	7651.5	9899.5	9394	—	13.9
5	119.5	4951.9	11173.2	—	—
6	1740	97	74.5	15	13.9
7	870	89	558.3	—	—
8	10	15	782.8	10.4	—
9	46	1	318	—	—
10	1470	151.9	548	—	—
11	541	164	827.1	—	—

M (mg/24 h) per hour E (mg/24 h) Total catecholamines (%) I VI I 17 Adrenosteroids (mg/24 h)

excreted in water and the increased volume required hemodialysis on her 10th hospital day because of renal failure and the retention of fluid. This lowered her plasma concentration of cathecholamines markedly (Table III) and nearly all the fluid infused during that time was excreted partially due to the dialysis. The pallor of her skin cleared appreciably during the procedure. However, she failed to respond to peritoneal dialysis and died in pulmonary edema 7 days later.

At autopsy a well-encapsulated pheochromocytoma

weighing 80 g. was found in her left adrenal gland. She had bilateral pleural effusion, pulmonary congestion and atherosclerosis. There were mild mesenteric hemorrhages around the 12th ribs and in the subcutaneous tissue of the mesenteric region. Renal failure was due to lower nephron nephrosis (Fig. 1). The arteries to the renal cortex showed moderate thickening and hyaline degeneration and the glomerular capillaries were congested and had hemorrhaged into Bowman's spaces. There was also extensive central hilar necrosis in the lower

Build	Pharmacologic tests	Posture x-ray film	Location of tumor	Comment	Fall x up
Average	—	—	Left	Acute tubular necrosis Congestive heart failure	Fluid Normotensia
Obese Thin	I R	IVT IVP	Left	Neurofibromatosis	Normotensia
Obese Thin	R H	Torso 0	Right Right Right	Severe paroxysmal symptoms Normal AE excretion	Normotensia Normotensia
Obese	R	0	Bilateral	20 pound gain in weight in preceding few years	Normotensia Normotensia
Thin	H and R	IVT	Right	Increasing intra-abdominal pressure caused attacks	Negative H test
Average	H and R	—	Right	Hyperventilation induced attacks Malignant	Normotensia and well 9 yr later
Thin	B	—	Left	Mild worse in afternoon	Normotensia 10 yr 30 pound gain in weight
Thin	—	—	Right	Stooling ceased 12 h Mild CV	Normotensia 7 yr later

CV = cardiovascular

Table III The effect of hemodialysis on plasma levels of catecholamines and their excretion in the dialysis fluid after the procedure

	NE (ng/L)	NE (ng/L)
A Plasma		
I red state	5.6	72.4
I o red state	1.9	21.4
B Dialy fluid		
(after hemodialysis)	0.0 and 0.5%	0.9 and 1.6%

B plasma level
I red state level

Case 2 A 74-year-old white woman, as known to us, been mildly hypertensive for 2 years before she sought medical advice on April 14, 1959 for a throbbing frontal headache and nervousness of recent onset.

On physical examination her pulse rate was 60 per minute and the blood pressure was 200/120 mm Hg. She was obese, weighing 113 pounds and had a mild proportion. Her skin was cold and clammy. She had a pulse that she had seen 11 mm Hg.

Her pulse rate was 60 per minute and the blood pressure was 200/120 mm Hg. She was obese, weighing 113 pounds and had a mild proportion. Her skin was cold and clammy. She had a pulse that she had seen 11 mm Hg.

The left suprarenal gland was removed November 1959. It contained a benign solid yellowish mass tumor that weighed 61 grams. The gland pressed on the aorta, crura of the diaphragm, and the left renal vein.

Case 3 A 18-year-old white woman was hospitalized in December 1951 because of severe headaches, vomiting, and tingling in the extremities. These symptoms were paroxysmal and had been present for about 4 years. Deep breaths were caused by exertion precipitated attack.

Her pulse rate ranged 90 per minute. During an attack her blood pressure rose to 260/150 mm Hg from an average baseline of 120/80 mm Hg. She was slightly agitated and was of average build. Her skin was moist but was of normal temperature. Her blood pressure rose to 260/160 mm Hg after administration of 0.5 mg of hypertensive drug. This was

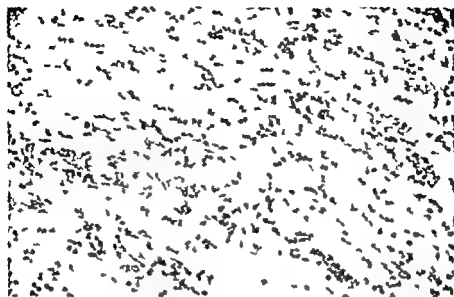


Fig. 1. C. 1. Adrenal tubular necrosis at autopsy. There is destruction of tubular epithelium with flitting up and down effort at regeneration by the remaining viable cells. Many granular casts are evident.

we managed to the same symptoms which she had when he was admitted 150 milligrams of phenyltinnin promptly lowered her blood pressure to 155/65 mm Hg with relief from her symptoms (Fig. 2). A triangular shadow distorted the upper pole of the right kidney on an intravenous pyelogram.

A patient with pheochromocytoma weighing 150 lb. and 5 ft. 10 in. in the right adrenal area. It was removed with great difficulty because it was adherent to the inferior vena cava, the liver and the diaphragm. The tumor appeared to be malignant on histologic examination. Her convalescence was unremarkable and she was asymptomatic and normotensive 9 months later.

Comment

Pheochromocytoma are likely to be overlooked in patients whose symptoms and hypertension lack a paroxysmal pattern. Three of the patients whose clinical features are summarized in Table I maintained a persistent hypertension. Their overall clinical pictures, however, did have many features to suggest the correct diagnosis. It usually remains necessary to confirm these suspicions with pharmacologic tests or catecholamine determinations.

The presence of obesity is likely to bias the clinician. In 1936 Kastle and associates¹⁴ commented: "We have yet to see an obese patient with a pheochromocytoma. However obesity has been reported in association with these tumors."¹⁴

Clinical features suggestive of Cushing's syndrome were present in a few of these patients.^{14,15} Three of our subjects were overweight (Cases 2, 4, 6, Table I) but none of them appeared to have the Cushing syndrome. However one patient excreted an excess of 17 ketosteroids (Case 2, Table II).

Increased adrenal cortical activity is not a feature of the usual nonobese patient with pheochromocytoma. Yet adrenal cortical hyperplasia^{16,17} and adenoma¹⁷ have been reported in association with these tumors. In 3 other instances tumors of the adrenal cortex have functioned in the manner of a pheochromocytoma.¹⁸⁻²⁰ An increased serum level of 17 hydroxycorticosteroids has been described in a patient who had a functioning tumor of the ovary in of Luckert and that increased further after removal of the tumor.²¹ Although the relationship between adrenocortical and medullary function remains obscure, there is experimental evidence which suggests that catecholamines accelerate 17-21 dihydroxycorticosteroid synthesis from progesterone in incubations of adrenal cortical homogenates.²² Perhaps the obesity and hypercorticism occasionally found in association with a pheochromocytoma are results of cortical stimulation by the prod-

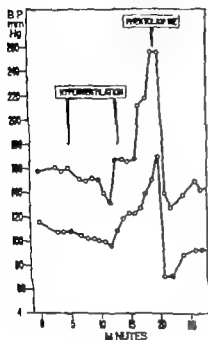


Fig. 2 Case 8. The effect of hyperventilation on the blood pressure and the prompt response to phenolamine.

ucts of the medullary tumor. It is certainly not valid to exclude pheochromocytoma on the basis of obesity.

The acute tubular necrosis that occurred in Case 1 is a rare complication of pheochromocytoma. Carpenter and Kavin¹ could find reference to only 3 other reports prior to their patient in 1961. Lower nephron nephrosis has also occurred in a patient who had an adrenal cortical adenoma and an increased rate of excretion of catecholamines.

The cause of the tubular lesions in pheochromocytoma remains uncertain. Oscillations of blood pressure to hypotensive levels, such as occurs during crises, may be a contributing factor, especially if renal blood flow has become impaired because of atherosclerotic arterial changes caused by prolonged exposure to hypertension. Postmortem studies performed in Case 1 suggest that ischemia due to arterial spasm played a major part in the necrosis of the renal tubules. Roentgenographic pictures were taken of the kidneys after arterial injection with 10 per cent vinyl plastic with bismuth oxychloride (Fig. 3 C). Her kidneys showed marked cortical ischemia and arterial spasm when compared with a healthy control kidney.

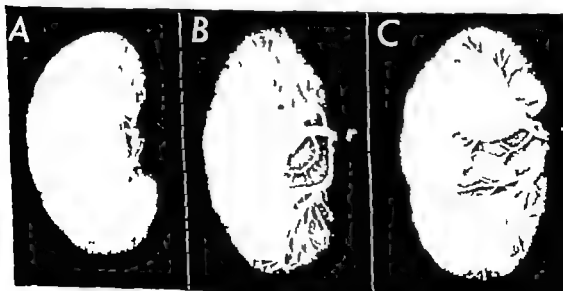


Fig. 3. Renal arteriograms from kidneys removed from (A) a healthy individual, (B) patient with posthypertensive acute tubular necrosis, and (C) Case 1. Note the marked cortical ischemia and arterial spasm.

treated in the same fashion (Fig. 3A). This is not a feature of acute tubular necrosis as is evident from Fig. 3B. This patient died from acute tubular necrosis that resulted from prolonged shock. The histologic changes found in the arteries of the kidney in Case 1 were not sufficient to account for the findings depicted in Fig. 3.

It would seem that this patient's kidneys were involved in a vicious circle. A high circulating level of catecholamines caused ischemic damage to her renal tubules. The renal failure that followed caused further retention of the noxious pressor amines. Hemodialysis proved to be partially effective in correcting this effect.

Case 2 had neurofibromatosis. The association of this neurocutaneous disorder and pheochromocytoma is well established. Over 40 instances in which these disorders coexisted have now been reported.⁴⁻¹¹ Neurofibromatosis is readily diagnosed when hypertension is present; it should alert the clinician to the possibility of a coexisting pheochromocytoma.

The danger of triggering an attack by manipulation of the tumor during operation is well known. Normal physical activities may also compress the tumor and express catecholamines into the circulation. Provocations were caused in our patients by the lifting of heavy objects by lying in certain positions (Case 7) and by stooping forward (Case 10). A dramatic response to physical compression was illustrated in Case 5 (Fig. 2). The tumor was adherent to the patient's diaphragm in situ *venotomica* and liver. The movement of her diaphragm during hyper-ventilation compressed the tumor which resulted in severe hypertension.

Catecholamine dynamics in pheochromocytoma

The total 24 hour urinary output of catecholamines in 7 patients who had pheochromocytoma varied from 281 to 11,175 per cent of the upper limits of normal excretion (Table 13). The day to day excretion did not fluctuate widely. There was no apparent relationship between which catecholamine predominated in the urine and the severity of the hypertension, nervousness, body build, metabolic or levels of blood sugar.

The rate that a pheochromocytoma attains before discovery depends on the symptomatology it generates. This is influenced by many factors. One element is the number of secreting tumor cells. Cystic tumors have relatively few functioning cells and reach a large size before they are discovered. Symptoms are also dependent on the rate at which the tumor releases catecholamines into the circulation. This is extremely variable and recently it has been shown¹² that up to 90 per cent of the catecholamines produced by a pheochromocytoma may be ineffective because they are metabolized without being released into the circulation. Such

ineffective catecholamine synthesis was observed in two malignant tumors.¹³ This rapid degradation of catecholamines is reflected by an increased excretion of such metabolites as 3 hydroxy-4 methoxy mandelic acid (VMA), normetephrine and metephrine. Only 0.3 to 4 per cent of the catecholamines infused intravenously may be recovered in the urine.¹⁴ If this is analogous to the intravenous release of catecholamines from a pheochromocytoma, urinary catecholamine values will represent only 0.03 to 0.4 per cent of the amount made in tumors that have a high rate of degradation *in situ*.

There is also a wide individual variation in sensitivity to catecholamines. Most patients with pheochromocytoma are relatively insensitive to high circulating levels of the products of the tumor. Occasionally hypertensive crises occur in patients while catecholamine excretion does not exceed normal limits.¹⁵ Such patients show an unusual sensitivity to infused catecholamines when studied after removal of the tumor. Patients who have essential hypertension are also more sensitive to infusions of NE than are normotensive control subjects.¹⁶

Thus the systemic effects of catecholamines and their excretion by a pheochromocytoma are governed by many factors. These include the amount of functioning chromaffin tissue present, the balance between release and degradation of catecholamines, and the sensitivity of the individual patient to their pharmacologic actions. It is evident from this complexity of factors that no chemical test can be used as a screening test to screen

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Cardiac output in erythrodermic skin disease

Gustaf C. Lund MD*

Herbert L. Kronthal M.D.

Robert G Cronase MD***

Baltimore Md

Patients with extensive erythrodermic skin disease may present with dyspnea, peripheral edema, cardiomegaly, hepatomegaly, wide pulse pressure and elevated venous pressure.^{1,2} These findings have been interpreted by some investigators as indicative of high output cardiac failure.^{1,2} It is conceivable that the increase in circulation to the skin and subcutaneous tissues in extensive skin disease characterized by erythroderma would result in a significant increase in cardiac output. Fox and associates² measured cardiac output in such patients and found high values in 2 patients who had psoriasis or exfoliative dermatitis. The opportunity to observe a patient who had congestive heart failure with clinical signs of high cardiac output associated with a severe exacerbation of psoriasis prompted us to measure cardiac outputs in patients with erythrodermic skin disease. This is a report of our findings in 6 patients.

Materials and methods

Six male patients with pruritus or exfoliative dermatitis were studied. The pa-

tients are described in Table I and in Fig 1 an illustrative case demonstrates the extent of disease present in these patients. All of the patients had at least 50 per cent of the skin area involved and those with exfoliative dermatitis had disease involving almost all of the body surface. Three patients (J C, E M and V M, Table I) had congestive heart failure when first seen. One patient (E M) had definite evidence of underlying heart disease. Causes of high cardiac output such as fever, anemia, hyperthyroidism, hypoxemia, Paget's disease of bone, arteriovenous fistula and beriberi heart disease were ruled out. In most patients cardiac outputs were measured soon after acute exacerbations of chronic psoriasis or the onset of exfoliative dermatitis and usually before their skin disease was treated.

The patients were not premedicated. After the insertion of a venous catheter and an arterial needle the patient was allowed to rest for 15 minutes. Cardiac output was measured using dye dilution by injecting indocyanine green into a peripheral vein and sampling from a brachial artery. Car-

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A n n o u n c e F a m i l y o f D e r m l o g y T h j i l l p h i l v e r r y C h e m i c a l M e d i c i n e

Table 1. Summary of clinical findings and laboratory results in 6 patients with erythroid toxic skin disease

Patient	Age (y)	Disease	Extent of disease (%)	Blood pressure (mm Hg)	History and physical	Chest x-ray finding	ECG	CI (L/min/m ²)	SI (ml)	HR (per min)
J.B.	33	Idiopathic	60	130/70	—	Normal	Normal	3.4	83	80
J.C.	39	Idiopathic dermatitis	90	140/80	Dyspnea, orthopnea, edema (+) 2+	Normal	Normal	3.8	95	87
W.M.	39	Idiopathic	55	110/70	Hypertension, edema 2+	Normal	Normal	6.0	99	96
J.W.	44	Idiopathic dermatitis	90	130/70	—	Normal	Normal	4.9	95	90
L.M.	62	Idiopathic	65	110/90	Dyspnea, orthopnea, edema 1+	Cardiomegaly	Normal	4.4	96	97
A.M.	73	Idiopathic dermatitis	85	150/80	Dyspnea, orthopnea, edema 1+	Cardiomegaly	Normal	5.5	103	95

Red cell count (x 10⁶/mm³) Hemoglobin (g/dl) Hematocrit (%) Reticulocyte count (%) Total leukocyte count (x 10⁹/mm³) Total platelet count (x 10⁹/mm³)

cardiac output was calculated by the pooled sample technique.⁴ Duplicate determinations were made in each patient and the average of the two results is reported. The duplicate values varied from the average by ± 7 per cent or less.

Results

The results are summarized in Table 1 and the cardiac outputs of our patients and the cardiac output in normal man are compared in Fig. 2. The normal values represent determinations of cardiac output in patients with normal hearts who have undergone cardiac catheterization in this institution and compare well with the results obtained in normal young men by other investigators.^{1,5} Cardiac output was significantly elevated in 4 patients. Stroke volumes were also elevated but to a lesser degree indicating that some of the increase in cardiac output was secondary to an in-

crease in heart rate. Although none of the patients had tachycardia their pulse rates were above normal resting values. This observation is similar to the findings in other diseases associated with high cardiac output.^{10,11}

Two patients were studied again.

P.M. A 62-year-old man with atherosclerotic heart disease and a long history of severe psoriasis was restudied after 9 weeks of topical therapy with triamcinolone acetonide and occlusive plastic wrapping produced dramatic improvement in his skin disease. When he was first seen heart failure was present. About 65 per cent of his skin was involved by typical psoriatic plaques and marked erythema. His cardiac output was 9.1 liters per minute. After successful treatment of the psoriasis scaling was minimal, erythema was absent and much of the skin was smooth and pliable (Fig. 3). Without any changes in his diet

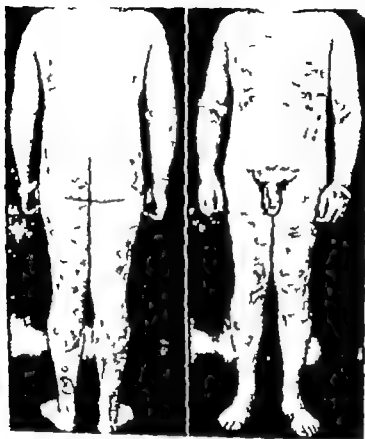


Fig. 1 Photograph of J. B. 33 illustrating the extent of disease. The patient shed about 60 per cent of his body surface involved by psoriasis.

activity or medications the signs and symptoms of heart failure regressed. Cardiac output was measured again and had fallen to 5.0 liters per minute (Fig. 2). A concomitant increase in circulation time and decrease in venous pressure supported the clinical impression that heart failure associated with high cardiac output improved when the psoriasis responded to therapy (Table II).

W. W., a 39-year-old man, had severe exacerbation of long-standing psoriasis when first studied. Typical psoriatic lesions associated with scaling and generalized erythema involved 55 per cent of his skin. Pitting pretibial edema and hepatomegaly were present but it was not certain that he was in heart failure. Cardiac output was 9.5 liters per minute. Nine months later, after intensive treatment with intermittent systemic corticosteroids and methotrexate in addition to topical medi-

cations, he was much improved. Although the skin was still somewhat erythematous there was no scaling and the skin was soft. Pretibial edema was not present. Cardiac output at this time was 5.1 liters per minute (Fig. 2). Circulation time increased suggesting a decrease in the speed of circulation (Table II).

Discussion

It has been estimated that the blood flow to the skin normally represents between 5 and 9 per cent of the total cardiac output. Although direct measurement of the blood flow to the skin is difficult, a few observations demonstrate that the cutaneous circulation is very flexible. Blood flow to the finger which has a high surface area to volume ratio has been shown to increase almost 100 fold with a change from a cold to a hot environment. In human adaptation to work in hot environments, a large

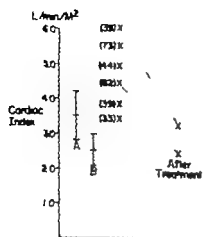


Fig. 1. Comparison of the cardiac output or indexed heart rate of patients with erythrodermic skin disease and normal men. The cardiac indexes of the patients are indicated by X and their ages are given in parentheses. A is the range of cardiac index in normal young men and B is the range of cardiac indexes in normal men over the age of 60. Two patients, 62 and 73 years old, have cardiac indexes which are more strikingly elevated than compared to those of normal men of the same age. Two patients, 39 and 67 years old, studied 6 months after successful treatment of their skin disease demonstrated decrease in cardiac index to normal values.

increase in circulation to the skin and subcutaneous tissue is brought about by an increase in blood volume and an elevation in cardiac output. The magnitude of these changes can be appreciated when the heart fails to maintain or to increase this output and serious hypotension occurs as it does in some patients with heat exhaustion.^{14,15} Studies of the capillaries in normal and diseased skin demonstrate significant increases in the size of these vessels in several pathologic conditions.

In diffuse skin disease characterized by erythrodermia increased circulation to the skin can be appreciated clinically. It is conceivable that this increased circulation would result in an increase in cardiac output. The fact that cardiac output is elevated in some patients with erythrodermia in disease supports this hypothesis. The cardiac outputs of 4 of our patients were elevated to the same order of magnitude as those reported in severe anorexia nervosa, perthyroidism, and Paget's disease of bone.^{16,17} A disease in which high cardiac output has been documented and high

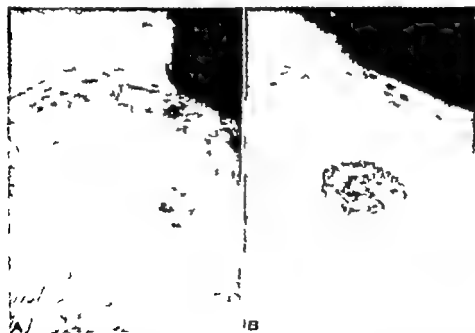


Fig. 2. Photograph of representative area of 11/63-year-old patient before treatment. Cardiac output was 9.5 liters per minute. B. The same area after 9 weeks of therapy. The result is an improvement and decrease in scaling and erythema. Cardiac output had fallen to 5.0 liters per minute. The small porietic plaque in B did not respond to successful therapy and was treated locally by curettage. This is a clinical example of the Koebner phenomenon. No other such plaques were present.

Table II A comparison of hemodynamic findings in 2 patients before and after successful treatment of extensive psoriasis

Patient	Parameter	Before treatment	After treatment
E M	Circulation time (sec)	32.0	20.0
	Venous pressure (mm of saline)	19.0	12.0
	Cardiac output (l./min)	9.1	5.1
	Cardiac index (l./min/m ²)	4.4	2.4
W M	Circulation time (sec)	11.0	13.5
	Cardiac output (l./min)	9.5	5.1
	Cardiac index (l./min/m ²)	6.0	3.2

Approximate (approximate) = seconds of time to beat of artery

output cardiac failure has been reported. Further evidence that cardiac output is elevated as a direct result of diffuse erythrodermic skin disease is obtained from the studies of 2 patients during exacerbations and remissions of severe psoriasis. Cardiac output decreased significantly, circulation time increased and signs and symptoms of heart failure regressed when their skin disease responded to treatment.

Brandfonbrener, Landowne and Shock¹ have shown that there is a decrease in the cardiac output of normal man as age increases. They found a mean cardiac index of 2.45 liters per minute per square meter of body surface area in normal men over the age of 60 years. Two of our patients, ages 62 and 73, had cardiac outputs which were more strikingly elevated when they were compared to those of normal men of the same age (Fig. 2).

The fact that cardiac output is increased in some patients with erythrodermic skin disease appears to be clinically important. Several investigators, reviewing large series of patients with exfoliative dermatitis and other erythrodermas, point out that these diseases have a high mortality rate, approaching 30 per cent in some series.^{2,3} Edema, hepatomegaly and tachycardia in the absence of fever are associated with these diseases and are often unexplained. The mode of death is not well understood but heart failure is occasionally described. It seems to be reasonable to conclude that

high-output cardiac failure may be an important factor in the morbidity and mortality of erythrodermic skin disease particularly in patients with underlying heart disease.

Summary

Cardiac output was measured in 6 patients with erythrodermic skin disease. Four patients had a significant elevation of cardiac output. Satisfactory treatment of psoriasis in 2 patients resulted in a decrease in cardiac output and regression of heart failure. The significance of these observations is discussed.

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An evaluation of the cardiac index

Harold Smulyan MD*

William I Vincent MD

Edomporn Asakemsant MD

Richard P Cudd MD

Robert H Fish MD

Syracuse NY

The body surface area taken from the Boothby and Sindisford nomogram as an estimate of body size is widely used to narrow the normal range of many physiologic measurements. One such measurement the cardiac output has a large scatter in normal subjects because of the variability inherent in the methods used and the physiologic variations in the subjects studied. It would seem that conversion of cardiac output to cardiac index would effectively reduce the scatter of normal cardiac output measurements by accounting for one of the variables body size. The cardiac index has been utilized in this way for many years but its value has rarely been questioned. It is the purpose of this study to collect information in regard to the use of body surface area as a ratio standard for the cardiac output to attempt to judge from this evidence whether such a practice is worth while and if it is found to be unsatisfactory to attempt to develop a more useful method of correcting cardiac output for body size.

Historical background

The first extensive work in the measurement of body surface area (BSA) was

done by Meek in 1879.¹ He made measurements in 6 adults and 10 children using various methods such as marking the body in geometrical patterns winding strips of paper about the limbs and cutting out and weighing pieces of paper which covered irregular portions of the body. He then derived a formula the use of which produced results within 7 per cent of his actual measurements. This formula employed the two thirds power of the weight since the surface area of two objects of the same shape are to each other as the two thirds power of the volumes. Although several attempts were made to improve it Meek's formula was used for 37 years.

When the Russell Sage Institute of Pathology decided to express calorimeter results for the study of the basal metabolic rate in terms of BSA they assigned the problem of measurement of BSA to an electrical engineer Delaheld DuBois. The results of his efforts were published in 1915. Five subjects were studied (1) a 36-year old cretin short and stocky with a mill hand (2) a 21 year old subject slightly stout (3) a 22 year old subject tall thin and bony with little fat (4) a 32 year-old subject tall and of average

From the Department of Medicine, St. L. and S. (St. Louis) and St. L. and S. (St. Louis) and St. L. and S. (St. Louis).

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Address reprint requests to Dr. Smulyan.

Reprint requests to Dr. Smulyan, St. L. and S. (St. Louis).

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build and (3) female very short and very fat (no one given). These patients were dressed in tightly fitted underwear, thin socks, thin cotton gloves and a section of the leg of a knitted undersuit pulled over the head and neck. Strips of manila paper were then pasted on until a flexible but inelastic covering of the body was completed. This covering was cut off with scissors and a mold of each section made by coating the inside with melted paraffin. The molds were then cut into small pieces and placed over sheets of weighed photographic paper which were exposed, cut out and weighed. Hands were measured by making paraffin molds over cotton gloves and other difficult areas such as the genitalia between the toes behind the ears etc. were traced separately. Usually only one arm and leg were measured. The method was thought to be accurate because repeat measurements of the bottom of a dish agreed within 0.1 per cent, two halves of one subject's body agreed within 0.5 per cent and the measured surface of a bowling ball differed only by 0.13 per cent from the area calculated from the diameter.

The body was considered in regions—head, arms, hands, trunk (including neck), thighs, legs and feet. For a given region various measurements of length and breadth were taken and their products related to the measured area of that region. A formula was then assigned which consisted of the product of the length-breadth (or girth) and a constant. Each was chosen to provide with the least variation the closest approximation to the measured area for the region. The BSA's were then predicted to be the sum of the calculated areas of all the regions. This was referred to as a method using the linear formula.

In 1916 Sawyer, Stone and DuBois³ studied 7 more subjects in similar fashion: (1) a 21-month-old child with rickets, small, pigeon-breasted who had died of pertussis; (2) an 18-year-old male emaciated diabetic; (3) a 76-year-old female sculptor's model; (4) a 21.5-year-old male tall and thin; (5) a 43-year-old male who had lost both legs in a railroad accident (attempts atrophied face fit); and (6) a 34-year-old male who had lost both legs in an automobile accident. The seventh and later three subjects were excluded

because they had been covered with idiosyncratic tape which it was suspected had stretched. This left 3 subjects whose measurements were used. Subject No. 5 had the head mold omitted and Subject No. 6 had measurements of the trunk and thighs only. In Subject No. 2 an error was made in the measurements for the location of the suprasternal notch. This was discovered when the measured and calculated BSA did not check. Unfortunately the patient had died and could not be re-measured. The authors therefore took measurements from several others of his build and used the average of these values in the formula for the area of the trunk.

In the same year⁴ DuBois and DuBois discussed the difficulties in making the 19 measurements of length and girth necessary for the linear formula. They tested various other formulas using height and weight only and selected constants which gave the least variation between measured and calculated areas. Their final formula was

$$BSA = \text{Weight}^{0.725} \times \text{Height}^{0.725} \times 71.84$$

Use of this formula was associated with an average error of 1.5 per cent and a range of errors within ± 5 per cent.

In 1921 Boothby and Sindisford⁵ developed from the DuBois formula the nomogram used today which relates height, weight and body surface area. Berkson and Boothby⁶ later affirmed the fact that the regression line of observed data for basal metabolic rate vs BSA was very close to that of a ratio standard. In the scatter plot of one variable against another a ratio standard line can be defined as one which is drawn through the origin of the graph and the intersection of the mean values for the two groups. These authors also tried to improve the relationship by using height and weight alone and several other exponents of height and weight. None of these approximated a ratio standard as well as the BSA calculated from the DuBois formula. This relationship suggested to Collip⁷ that BSA as calculated from height and weight was an indirect measure of the active or metabolizing body area and predicted the ratio of cardiac output (CO) to BSA to be reasonably constant. He studied 50 more

mal subjects under stringent basal conditions using the acetylene method for measuring CO and found this to be true. He suggested therefore that the cardiac output be corrected in this way and be called the cardiac index.

Several other workers have also attempted to study this problem. Starr and associates² using the ballistocardiogram Taylor and Tiede¹⁰ using the ballistocardiogram and the acetylene method and Brotmacher and Deuchar¹¹ who did a search of the literature all found low correlation coefficients between CO and BSA. Jegier and associates¹ using an ear oximeter on lightly anesthetized subjects found a high correlation. Their subjects were children ranging in age from newborn infants to adolescents. The high r values found can be accounted for by the extremely wide range of body sizes studied but the study does not resolve the problem in adults in whom the range of BSA is considerably smaller. Reeves and associates¹² in studying 63 subjects free of cardiovascular disease ages 2 to 45 years thought that the relationship between BSA and CO was biologically obscure. These authors suggested that CO be related to SA difference to account for differences in physiologic state but this suggestion would not reduce the variability secondary to differences in body size. In summarizing this problem in his recent book Crompton¹³ stated that there was little basis for using BSA as a ratio standard in preference to weight or weight raised to a fractional power.

Materials and methods

In order to investigate the relationship of CO to BSA under basal conditions 22 male patients at a Veterans Administration Hospital were studied. These men were carefully selected for the absence of abnormalities or the administration of drugs known to influence the circulation and were considered for purposes of this study to be normal. All subjects were requested with the procedures on the day prior to the study and were fasted after the evening meal. They remained in bed the following morning until 8 AM when they were brought to the laboratory at which time the patients were made comfortable in

the supine position and with the use of local anesthesia an 18 gauge Courmand needle was inserted into a brachial artery and a No 18 intravenous needle was placed in the opposite arm. Thirty minutes of quiet rest was then interrupted only by measurement of auscultatory blood pressures and heart rates at 10-minute intervals. After this one half hour of rest oxygen consumption and CO production was measured by collecting expired air in a 120 liter Collins gasometer. During this collection the cardiac output repeat blood pressures and heart rates were obtained. The patients then rested 10 more minutes at the end of which time all measurements were repeated.

Concentrations of oxygen and CO in the expired air were measured by the Scholander technique and oxygen consumption CO production and respiratory quotient were calculated in a standard manner. Cardiac output was determined by means of the indicator-dilution technique of Hamilton and Stewart using radioiodinated (¹²⁵I) human serum albumin as the indicator and a timed 2 second interrupted arterial sampling technique.¹ At the conclusion of the study the height and weight were measured on a standard hospital scale and the BSA was determined from the Boothby and Sandiford nomogram.¹

In order to insure that these patients were stable subjects were only included in this group when their first and second measurements were reproducible that is there was (1) less than 10 mm Hg variation in systolic blood pressure (2) less than 4 beats per minute variation in heart rate (3) less than 0.15 variation in measured respiratory quotient and all respiratory quotients were less than 1.0 and (4) less than a 15 per cent variation in oxygen consumption. The CO values of all subjects who met the above mentioned criteria were used and all other were rejected for this analysis.

The data on height weight BSA and CO from a second group of 60 normal subjects selected from the hospital population in the same way were taken from measurement made preliminary to other investigations carried out in this laboratory in the last few years. Although these also

Table 1 Mean and reproducibility of basal values $N = 22$

	Age (yr)	Height (m)	Weight (kg)	BSA (M^2)	BI (mm Hg)			
					I		II	
					S	D	S	D
Mean	39	1.5	71.4	1.86	119	71	117	71
SD	7	7.6	15	0.21	12	9	11	8
Mean-Difference	—	—	—	—	—	—	2.7	7
SD of difference	—	—	—	—	—	—	2.6	3.5
Coefficient of variation of difference (%)	—	—	—	—	—	—	2.2	4.9

Statistical analysis: coefficient of correlation = 0.92, $P < 0.001$.
 Coefficient of correlation = 0.92, $P < 0.001$.

were normal subjects no attempt was made to insure a basal state as in the previous group. The data from this non-basal group was used for comparison with the data from the basal group.

In addition to the values from the 92 normal subjects information in regard to CO and BSA was taken from a detailed search of the literature on 324 normal subjects.¹⁶⁻¹⁸ Making a total of 406 pairs of data. When available age, weight and height were also recorded. In these references when both Fick and indicator dilution measurements of CO were made in the same subjects the indicator dilution COs were taken when only the Fick method COs were recorded these were used when duplicate determinations of CO were noted only the first of the pair was used. These data were divided into two groups—basal and nonbasal. When the information in the references indicated that the subjects were studied fasting, without sedation shortly after arising, and with an attempt to allow quiet rest prior to the measurement the values were assigned to the basal group. Other data were assigned to the nonbasal group. We appreciate the fact that patients assigned to the basal group from different studies may vary in the degree to which a true basal state was attained. The information thus obtained was punched into IBM data processing card and analyzed

statistical analyses were calculated on a 1620 IBM computer.

Results

The data which characterize the 22 subjects studied under controlled conditions in this laboratory are set out in Table 1. The reproducibility of the blood pressure, oxygen consumption, heart rate and RQ is excellent because of the exclusion of subjects who were not steady with regard to these variables. With the steady and presumably near basal states defined in this way it is important to note that the CO values which were not included in the definition for inclusion in this group were also highly reproducible. The variability in CO measurement of approximately 4 per cent is probably close to the experimental error inherent in the method. Although it would appear to be difficult to attain a true basal condition in any subject whose brachial artery and intracubital vein have been cannulated the group seems to be close to that goal.

The measurements made in this series of patients were related to each other with the use of the correlation coefficient. The results are shown in Table II under the heading of Basal. This group provided a range of BSAs from 1.4 to 2.45 M^2 and of COs from 3.1 to 10.0 l/min . The correlation coefficient for CO vs BSA under these basal conditions was +0.43.

CO (L/min)		Heart rate per min		Vo (c/min)		RQ	
I	II	I	II	I	II	I	II
7.33	7.19	76	5	732	241	0.86	0.86
1.47	1.38	11	12	35	45	0.0	0.06
—	0.17	—	1.5	—	14.3	—	0.05
—	0.31	—	2.0	—	13.1	—	0.04
—	4	—	6	—	4.8	—	4

Table II Correlation coefficients—Sydney data

Relationships		Basal		Nonbasal	
		p value		p value	
CO	BSA	0.43	<0.05	0.38	60
CO	weight	0.43	<0.05	0.01	<0.005
CO	height	0.29	<0.10	0.01	<0.05
CO	age	0.1	<0.001	0.14	<0.5
VO	BSA	0.57	<0.001	44	—
VO	weight	0.61	<0.001	2	—
VO	height	0.31	<0.003	22	—
VO	cardiac index	0.51	<0.005	27	—
			44	—	—

Table III Correlation coefficients—Literature data

Relationships		Basal group		Nonbasal group		All p in	
		p	N	p	N	p	N
CO	BSA	0	<0.001	167	0.3	<0.001	.39
CO	weight	0.34	<0.01	60	0.41	<0.001	150
CO	height	0.3	<0.5	0.43	<0.001	131	0.39
CO	age	-0.0	<0.40	131	-0	<0.001	171
CO	weight	0.24	<0.01	60	0.40	<0.001	150
CO	height	0.3	<0	0.43	<0.001	154	0.39
CO	weight/height	-0.48	<0.01	0.3	<0.001	133	0.34
CO	weight and weight	—	—	—	—	0.44	<0.001
						160	160

at the lower limit of statistical significance ($p < 0.05$). It is of interest that body weight alone when compared to CO had an equally good correlation coefficient. The excellent coefficients of correlation found between CO and oxygen consumption and between oxygen consumption and BSA are well known. Again body weight had a correlation coefficient not significantly different ($p < 0.50$) from that of BSA when both were related to oxygen consumption ($r = +0.61$ and $+0.51$ respectively).

A plot of CO vs BSA in this basal group is shown in Fig. 1. This can be compared to a similar graph of the data taken from 60 normal patients when no attempt was made to insure a basal state (Fig. 2).

From these figures and from the data given in Table II it can be seen that the relationship between CO and BSA is similar in the basal and nonbasal states ($p < 0.50$). The standard error of estimate for both basal and nonbasal regressions in Table II varied from 1.34 to 1.56 L/min.

A similar analysis of all of the foregoing data plus the data taken from the search of the literature is presented in Table III. It is obvious that both the basal state and methodology of measurement of CO varied from laboratory to laboratory and these factors probably largely account for the lower r values found in all categories when comparison is made with the basal group from this laboratory (shown in Table II). In order to study further this

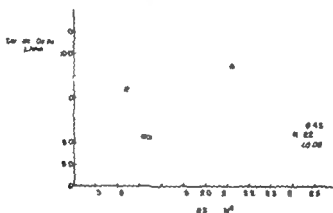


Fig. 1. Graph of cardiac output vs body surface area in 2 normal subjects under basal conditions.

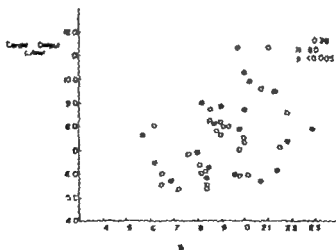


Fig. 2. Graph of cardiac output vs body surface area in 60 normal subjects under basal conditions.

over all scatter the data from each laboratory contributing to the 406 pairs of CO and BSA were analyzed using a chi square test for homogeneity. This test ($p < 0.001$) documented the homogeneity of the data and permitted the consideration of all of the data as a single group.

The literature values analysis of which is shown in Table III always included at least the CO and BSA. When height, weight and age were given this information was also recorded. The number of these values are therefore smaller than that of the BSA group. It is evident from Table III that the level of statistical significance found for the various correlations depends more on the size of the group than on the differences in the r values themselves. The correlation coefficients for CO vs BSA in the basal and nonbasal groups were not significantly different ($p < 0.20$) which suggests that division of the data into basal and nonbasal groups adds little information not found in the analysis of the entire group. For the entire 406 pairs the correlation coefficient for CO and BSA was +0.34, but the correlation coefficients for CO vs weight and height were +0.39 and +0.40 respectively. Attempts to improve these coefficients by correlating CO with height and weight raised to fractional powers were unsuccessful. Similarly unsuccessful was the attempt to correlate CO to the height weight ratio used as an estimate of stature. The best correlation ($r = +0.44$) was obtained when CO was related to height and weight in a multiple regression analysis. The standard error of estimate for all of the regressions in Table III ranged from 1.43 to 1.08 L/min.

The negative correlation of CO vs age ($r = -0.20$) has been previously shown⁴ and is again demonstrated here.

Discussion

The measurement of body surface area by Dubois in 1916 was a singular technical achievement. But when consideration is given to the fact that the entire measured group numbered only 10 patients in several of whom the measurements were incomplete the confidence placed in this measurement by many years of routine use seems to be unjustified.

Some of this early confidence arose from the observations that the regression line of the plot of large numbers of measured basal metabolic rates against BSA very nearly intercepted the origin of the graph and closely approximated the slope of the line which represented BSA as a ratio standard.⁴ Whether this relationship is fortuitous or has real physiologic meaning is unclear. In either case similar justification for use of the BSA as a ratio standard for the CO is not available.

In 1949 Tanner¹⁰ published a lucid description of the problems and assumptions made when a ratio standard is used. He pointed out that when any data is reported as an index such as CO/BSA there is an implied proportionality between the two parameters such that the regression line relating them is straight, intersects the ordinate or abscissa at or near the origin and has a slope similar to the ratio standard line. The greater the difference between the regression line of actual measurements and the ratio standard line the poorer that ratio standard will be. This is so because normal values at increasing distances from the means will be considered to be more and more abnormal when expressed as an index. This point is illustrated in Fig. 3 where the regression line representing all 406 measured values of CO and BSA is plotted on the same graph as the ratio standard. It can be seen that the regression line does not go through the origin. In addition the slope of the regression line is such that large normal subjects would be suspected of having abnormally low COs if normality were predicted on the basis of the ratio standard. The converse would be true of small individuals. Fig. 4 is a similar plot of CO vs weight which illustrates the same difficulty. Fig. 5 shows the opposite problem when the regression and ratio standard lines are plotted for CO vs height.

It can be shown statistically as described by Tanner¹⁰ that of the three the BSA ratio standard line is closest to its actual regression line. This method states that when the ratio of the coefficients of variation (CV) of the independent and dependent variables is equal to the correlation coefficient which relates them the regression and ratio standard lines are

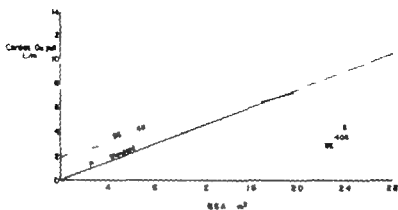


Fig. 3 Comparison of the regression line of the literature values for cardiac output on body surface area and the standard line for the same group

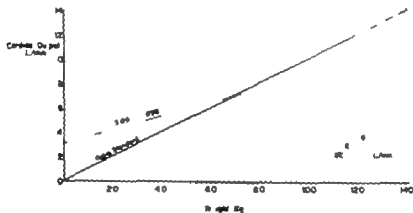


Fig. 4 Comparison of the regression line of the literature values for cardiac output on body weight and the standard line for the same group

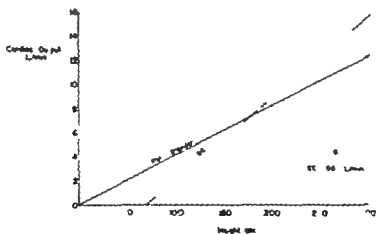


Fig. 5 Comparison of the regression line of the literature values for cardiac output on height and the standard line for the same group

identical. Commonly the greater the discrepancy between CV/CO and the r value the poorer the ratio standard will be. In the present study for the overall literature review

$$\frac{CV}{BSA} = 0.47 \quad r = +0.34$$

$$\frac{CV}{Height} = 0.734 \quad r = +0.40$$

$$\frac{CV}{Weight} = 0.712 \quad r = +0.40$$

The discrepancy between CV ratios and r is least when BSA is used and of the three it should therefore be the best ratio standard. Height and weight have higher correlation coefficients with CO but would clearly be poorer ratio standards because of the larger differences between their regression and ratio standard lines. At a 0.05 confidence level however all three regression lines differed from their respective ratio standard lines. These difficulties could be circumvented by using the regression formula for weight for example to predict the normal CO rather than using any ratio standard. Such a prediction would carry a standard error of 1.5 L/min. Since the use of multiple regression of height and weight on CO offers a somewhat higher correlation coefficient and since height and weight are already routinely recorded in most laboratories it would seem to be most reasonable to use the multiple regression formula for the purpose of predicting normal CO from body size. This formula calculated from the 160 values where these data were available is

$$CO (L/min) = -7.15 + 0.033 \times \text{weight (kg)} + 0.039 \times \text{height (cm)} \text{ with a standard error of } \pm 1.48 \text{ L/min}$$

Using this method a predicted CO on the basis of height and weight could be calculated. If the observed CO fell within ± 1.5 L/min of the predicted value the observed CO would be within one standard deviation of a group of known normal individuals with similar heights and weights. Judgments in regard to normality could be made on this basis.

It is unfortunate that of the 406 CO s reviewed in only 160 instances was height

and weight also recorded. Nonetheless this does represent a fairly large normal group with which others may be compared.

Ideally the technique of multiple regression could be extended to larger groups of normal subjects and include in addition to height and weight other determinants of the resting CO such as age, sex, heart rate and oxygen consumption. This analysis could then account for more of the variability seen but might become unwieldy for practical use. In any case the method described based on available data would seem to be a better method for assessing the normality of the CO than the use of the DuBois BSA as a ratio standard.

Summary

The value of using the body surface area to correct cardiac output for body size (cardiac index) has been studied in several ways. Its historical development has been traced and an attempt made to point out the strengths and weaknesses of the early data. Cardiac output and body surface area were correlated from 72 normal basal subjects and 60 normal nonbasal subjects from this laboratory. These results demonstrated a significant correlation of these variables in the basal and nonbasal states. It was also found in these subjects that when basal the cardiac output correlated equally well with body weight. Because the groups were small 324 normal cardiac outputs and body surface areas were taken from the literature and added to the previous groups totaling 406 such pairs for analysis. These results showed that the correlations of cardiac output with height and with weight were slightly better than that with body surface area. The importance of discrepancies between regression and ratio standard lines was discussed and it was found that although the body surface area was the best ratio standard for cardiac output of the variables studied it had a lower correlation coefficient and differed significantly from a regression line of normal values. It is suggested that the best solution is the avoidance of the use of any ratio standard but rather the prediction of the normal cardiac output from height and weight on the basis of a multiple regression an

values from a large group of normal subjects. Such a regression formula is presented.

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Experimental and laboratory reports

Incidence of ectopic beats as a function of basic rate in the ventricle

Jiok Hun M.D. Ph.D.

John DeLong B.S.*

David Miller*

Gordon K. Mor M.D. Ph.D.

[Lima, Pa.]

A number of clinical observations have shown that early ectopic beats occur in the ventricle more frequently when the basic frequency is relatively slow. For example, Langendorf and associates¹ reported that early ectopic beats develop more frequently after relatively long cycles in the ventricle in patients with atrial fibrillation. Zoll and Laminthang² and their co-workers observed that premature ectopic beats occur more frequently in the ventricle when the basic idioventricular rate is relatively slow in patients with complete A-V block, and the incidence of ventricular fibrillation is also higher at slower frequencies in these patients. When the ventricular rate was increased by electrical stimulation or by infusion of catecholamines³ the frequency of occurrence of premature beats decreased. Han and colleagues⁴ have recently suggested that the observed increase in the incidence of premature ectopic beats and fibrillation at slow ventricular frequencies might result from an increase in the degree of asynchrony of recovery of excitability in the ventricle at slow ventricular rates. Their experiments on dog ventricles have shown that the range of refractory period is greater and the fibrillation threshold is

lower in the ventricle at lower basic frequencies than at higher rates. The possible role of asynchrony of recovery of excitability in facilitating reentrant ectopic activity has been emphasized repeatedly in previous papers.⁴⁻⁶

To test the effect of basic rate on the incidence of early ectopic beats in the ventricle, the present experiments were performed on dog ventricles under some of the conditions which are known to facilitate the induction of ectopic activity and fibrillation in the ventricle.

Methods

Experiments were performed on mongrel dogs which weighed 10 to 20 kilograms and were anesthetized by intravenous injection of sodium pentobarbital in a dose of 3 mg per kilogram. Under artificial respiration the chest was opened in the midline and the heart was cradled in the opened pericardium. To permit observations at slow frequencies the S-A node was incubated in crushed ice. When a further reduction in the heart rate was necessary, the right or left vagus nerve was stimulated below a crushed area. Stimuli were square pulses of 2 msec duration at a frequency of 10 per second applied at a voltage sufficient to reduce

From the Medical Research Laboratories, University of Pennsylvania.

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the heart rate to about one cycle per sec and Stimuli were sometimes applied to the vagus nerve at a voltage sufficient to produce complete A-V dissociation.

The bipolar stimulating and recording electrodes were usually attached to the anterior surface of the left ventricle. Sites of stimulation and recording were separated by about 6 mm. A waveform generator was used to trigger a Tektronix pulse generator which delivered rectangular pulses of variable frequency, duration and intensity through an isolation transformer to the bipolar stimulating electrodes. At each basic cycle length the ventricle was driven by 2 msec pulses at two times the threshold voltage. When the ventricle was driven by paired electrical stimuli the waveform generator triggered two Tektronix pulse generators which in turn delivered paired pulses (S_1 and S_2) of 2 msec duration to the same pair of stimulating electrodes through the same isolation transformer. At each basic cycle length (S_1S_2) the interval between paired stimuli (S_1S_2) could be varied by

changing the delay between the pulse generators. Electrical responses of the ventricle were recorded on a Grass polygraph at a speed of 25 mm per second. The aortic pressure was recorded by means of a Statham pressure transducer attached to a cannula in the aortic arch.

In experiments in which the effect of coronary occlusion was studied the inferior descending branch of the left coronary artery was dissected free for a few millimeters near its origin in order to permit application of a clamp. Abrupt increases in aortic pressure were produced in some experiments by applying a clamp to the descending aorta just below the arch. In some experiments hypothermia was induced. After heparinization the blood from a femoral artery was passed through a coil immersed in an ice bath and returned to the dog through the femoral vein on the same side. The temperature of the blood in the heart was measured by a thermocouple introduced into the right atrium through the right external jugular vein.

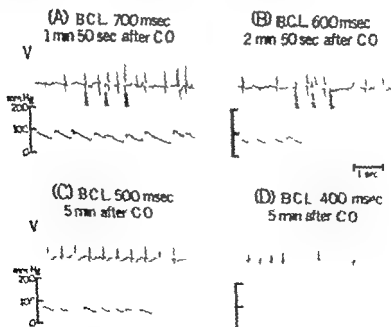


Fig. 1. Ventricle (V) and aortic pressure (mm Hg) responses at different basic cycle lengths (BCL) after coronary occlusion (CO) at different times after CO. The upper trace shows the ventricular action potential and the lower trace shows the aortic pressure. The bracket indicates the period of observation.

Results

Coronary occlusion For this group of experiments the stimulating and recording electrodes were attached to the anterior septal margin of the right ventricle on the edge of the area where ischemia extends during occlusion of the anterior descending artery. While the ventricle was driven at basic cycle lengths between 400 and 800 msec the anterior descending branch was clamped. If ectopic beats occurred the clamp was removed immediately. If no ectopic beats occurred the clamp was released after 5 minutes of occlusion. Repeat occlusion trials began about 20 minutes after the previous release of the clamp. The results of a representative experiment are illustrated in Fig. 1. In *A* the artery was occluded while the ventricle was driven at a basic cycle length of 700 msec; several ectopic beats occurred 1 minute and 50 seconds after the start of occlusion. In *B* the ectopic beats occurred 2 minutes and 40 seconds after the start of occlusion when the basic cycle length was 600 msec. No

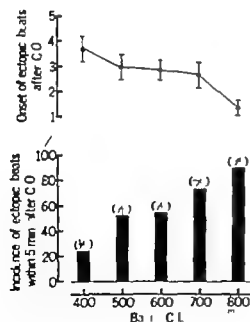


Fig. 1. Results of a representative experiment. *A*: Onset of ectopic beats after coronary occlusion at various basic cycle lengths. *B*: Incidence of ectopic beats within 5 minutes after coronary occlusion at various basic cycle lengths. The error bars represent the standard deviation of the mean.

ectopic beats occurred during 5 minutes of occlusion at basic cycle lengths of 500 msec in *C* and of 400 msec in *D*.

Similar results were consistently observed on repeated trials of coronary occlusion in 8 dogs; the cumulative data are shown in Fig. 2. Ectopic beats occurred within 5 minutes after the start of occlusion in 10 of 11 trials (91 per cent) at a basic cycle length of 800 msec with an average time of onset of 1 minute and 24 seconds. Ectopic beats developed 2 minutes and 40 seconds after the start of occlusion in 12 of 16 trials (75 per cent) at a basic cycle length of 700 msec, 2 minutes and 35 seconds in 9 of 16 trials (56 per cent) at 600 msec, 2 minutes and 38 seconds in 9 of 17 trials (53 per cent) at 500 msec, and 3 minutes and 44 seconds in 4 of 17 trials (24 per cent) at 400 msec. Analysis of variance indicates that the average time of onset of ectopic beats is a significant function of the basic cycle length at the level of $p < 0.05$.

Abrupt increase in aortic pressure The effect of abrupt increase in the aortic pressure was studied in 4 dogs, and the results of one of these experiments are shown in Fig. 3. While the ventricle was driven at various basic cycle lengths between 400 and 800 msec the descending aorta was clamped for 10 seconds and the incidence of ectopic beats was recorded. Repeat trials of aortic occlusion began about 5 minutes after the previous release. While the ventricle was driven at a basic cycle length of 800 msec in *A* the clamp was applied at the time indicated by an arrow. An early ectopic beat occurred about 3 seconds after the clamping when the aortic systolic pressure had increased to 195 mm Hg from the control of 100 mm Hg. A premature beat occurred about 3 seconds after the clamping when the aortic pressure increased to 200 mm Hg from 110 mm Hg at a cycle length of 700 msec in *B*. No ectopic beats occurred at cycle lengths of 600, 500 and 400 msec in *C*, *D*, and *E* respectively during 10 seconds of comparable increase in aortic pressure.

Similar results were observed in all 4 dogs; the cumulative results are illustrated in Fig. 4. Ectopic beats occurred in 13 of 14 trials (93 per cent) at a basic cycle of 800 msec, and with progressively decreas-

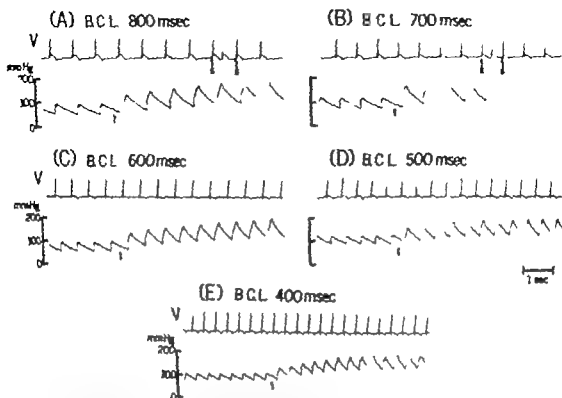


Fig. 3 Exp. 5 17-65. Premature ectopic beats induced in the ventricle by a sudden increase in the aortic pressure at different basic cycle lengths. The upper traces show ventricular responses and the lower traces show the aortic pressure. In the lower traces the time of the clamping of the descending aorta is indicated by an arrow.

ing frequency at higher driving frequencies. As shown in the upper part of the figure, the increase elevation of aortic pressure was quite similar at all basic cycle lengths.

Hypothermia. In the experiment depicted in Fig. 7, ectopic beats developed in the spontaneously beating ventricle when the temperature of the blood in the heart was decreased to 24.26°C. The ventricle was then driven by train stimuli for 30 seconds at each of several basic cycle lengths between 600 and 1 700 msec while the occurrence of ectopic beats was observed. Ectopic beats developed at basic cycle lengths of 1 700 and 1 000 msec in C and A but not at 800 and 600 msec in C and D. Repeat observations were made many times in 3 dogs and the cumulative data are shown in Fig. 6. The incidence of ectopic beats decreased progressively as the driving frequency was increased. No ectopic activity occurred at basic cycle lengths of 700 and 600 msec.

Paired pulse stimulation. The technique of paired pulse stimulation has been used to show the effective rate and to augment the force of contraction in the ventricle (12). Since the second pulse of a pair of stimuli is applied near to or in the vulnerable period of the ventricle, the possibility of development of ectopic beats has been a cause for concern. The frequency of development of ectopic beats was studied at different basic frequencies in the experiment depicted in Fig. 7. The threshold intensity of stimuli required to drive the ventricle with single stimuli of 2 msec duration was found to be 0.8 V. At each cycle length (S_1S_2) between 400 and 1 000 msec, the ventricle was first driven by single 1 sec stimuli (S_1) of 1 V; the coupled stimuli (S_2) were delivered to the ventricle during the refractory period of the basic responses and the S_1S_2 interval was then gradually increased until the ventricle responded to the second stimulus.

ectopic beats occurred in the ventricle more frequently when the basic rate was relatively slow. This was true whether the precipitating agency was coronary occlusion, sudden elevation of the aortic pressure or hypothermia.

Hin and co-workers⁶ demonstrated a

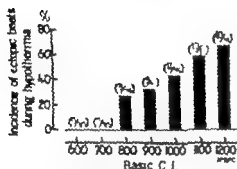


Fig. 6. The cumulative effect on the incidence of premature ectopic beats in the ventricle obtained from 183 trials of ventricular driving at different basic cycle lengths as is done during hypothermia.

greater range of refractory periods at various points on the ventricular surface when the basic frequency was low and they proposed that early ectopic activity could be the result of re-entrant excitation of already repolarized elements by the flow of current from still depolarized neighboring elements. Other studies also indicate that the difference in refractory periods in ventricular tissues increases as the heart rate decreases. For example, Moe and associates¹⁵ showed that the difference in refractory periods between the bundle of His and the right bundle branch is greater at slow frequencies of the heart and Moe and co-workers⁶ demonstrated that the duration of action potentials and the refractory periods of trabeculae eventually equal to those of papillary muscle at high driving rates, growth exceeded the latter at frequencies of 1 per second. These observations suggest that the likelihood of the development of re-entrant ectopic activity is enhanced not necessarily within ventricular muscle itself but perhaps at junctions.

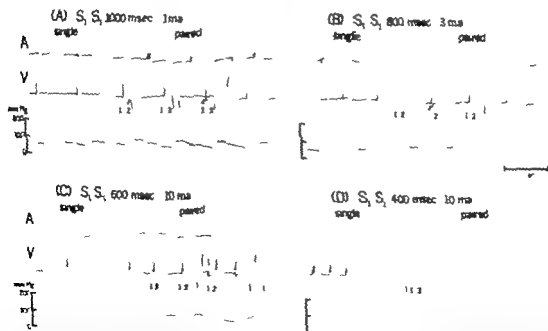


Fig. 8. Exp. 8, 4-63. Spontaneous ectopic beats developed after the second stimulated response during paired pulse stimulation at different cycle lengths of basic stimuli (S₁S₂). The upper traces show atrial responses, the middle traces show atrial responses and the lower traces show the so-called p waves. In the middle traces the coupling interval (the time interval between S₁ and S₂) is indicated by a vertical line. The traces observed during single-pulse stimulation at different cycle lengths were the same as those shown with a single pulse stimulation.

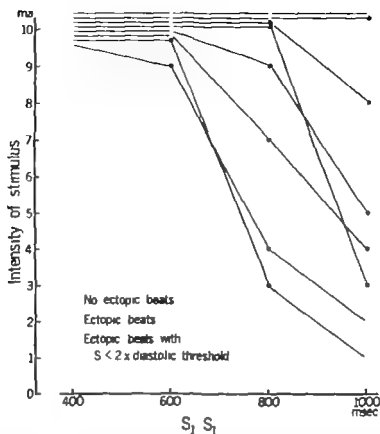


Fig. 8. The data obtained from 8 experiments on paired pulse stimulation. Basic cycle length or interval between two basic stimuli (S_1-S_1) is plotted on the abscissa in milliseconds and the intensity of stimulus used to initiate occurrence of spontaneous ectopic beat after the second stimulated response is plotted on the ordinate in milliamperes. Each solid line connecting four different points indicates the results of an individual experiment.

tions between two different tissues that is ventricular muscle and the specialized conduction fibers.

The present studies demonstrate that the hazard of inducing ectopic beats during paired pulse stimulation is increased at slow basic frequencies. Similar findings were reported by Langendorf and Pick.¹ In their clinical observations ectopic beats which were previously present during paired pulse stimulation at a relatively slow frequency could be abolished by increasing the rate of paired pulse stimulation. In the present experiments the stimulus intensity required to induce ectopic beat after the second stimulated responses was lower at low frequencies. In 2 cases the effective stimulus was less than twice the diastolic threshold, a strength reported to be safe.¹⁶ The results are in agreement with those of previous studies in which the ventricular fibrillation threshold was found

to be inversely related to the basic cycle length.⁴

Clinical situations requiring electrical stimulation of the ventricle are frequently associated with underlying conditions which may facilitate the induction of ventricular ectopic beats and fibrillation. For example, the presence of irregular perfusion of the ventricle associated with coronary heart diseases is known to contribute to increased asynchrony of recovery of excitability in ventricular muscle.⁸ It is particularly important therefore to select an optimum rate of stimulation in the presence of these additional contributing factors, and to consider the possible additional hazard involved.

Summary

The frequency of development of ventricular ectopic beat was studied at different basic frequencies under condition

which facilitate the induction of ectopic beats and fibrillation in the ventricle. Ectopic beats were more frequently induced by coronary occlusion sudden elevation of the aortic pressure and hypothermia when the basic frequency was low. The average time of onset of ectopic beats after the start of coronary occlusion decreased with a decrease in basic frequency. Ectopic beats developed more frequently after the second stimulated responses at slow rates of paired pulse stimulation. The stimulus strength required to induce such ectopic beats was much lower at slower frequencies of paired pulse stimulation. The results emphasize the importance of selection of an optimum rate of stimulation.

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Body surface isopotential maps in normal children, ages 4 to 14 years

Madison S Spack MD*

William P Silberberg

John P Bonneau MD**

Roger C Barr BS

I Croft Long MB PhD

Thomas M Gallie PhD

Judith B Galar MD

Andrew C Wallace MD

Durham NC

The ultimate diagnostic potential of electrocardiographic data obtained from the body surface will be realized only after extensive studies have been conducted to define the areas of the body which contain important information. The recent work of Faccardi¹ and Horan, Flowers and Brody² in human beings has demonstrated that the construction of total thoracic electrocardiograms (isopotential surface maps) provides information that is not available in tracings obtained with conventional electrocardiographic and vectorcardiographic lead systems. The major question concerning the clinical usefulness of looking at all of the information available at the body surface if this can be derived eventually will be answered only by knowing what information proves to be helpful in diagnosis and the management of the patient.

On the basis of the work of several

investigators¹ our group has undertaken an interdisciplinary endeavor to develop a practical method for generating isopotential surface maps in children and to develop a library of isopotential maps characterizing normal subjects and children with different cardiac conditions. This report presents (1) a digital computer method for constructing isopotential surface maps (2) a method for the calculation of zero potential on the body surface during various portions of ventricular activation and (3) the distribution of the body surface potentials for normal children between the ages of 4 and 14 years.

Methods

Twenty normal children between the ages of 4 and 14 years were studied. All patients were normal in history, general physical examination, auscultation, phonocardiograms, cardiac x-ray film, etc.

From the Department of Pediatrics (MS, JPB, RCB, ICL, JBG, ACW) and Medical Center (WPS, JPB, RCB, ICL, JBG, ACW) of the University of North Carolina at Chapel Hill, Chapel Hill, NC.

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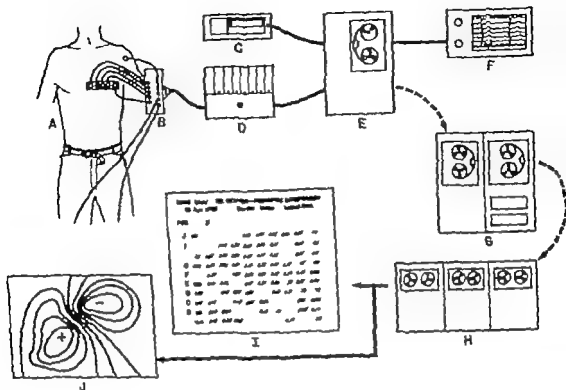


Fig. 1. Schematic representation of the techniques of acquisition and processing of data for the construction of isopotential surface maps. *A* Patient and lead connections. All children were studied in the supine position. Five thoracic electrocardiograms were obtained simultaneously in reference to the left leg electrode. After a block of 6 points were recorded, the electrode assembly was moved to a new position and this sequence was continued until 150 to 250 points had been recorded over the entire thorax. All thoracic electrocardiograms were recorded simultaneously with a reference lead. An impedance re-protractor was used to record respiratory and only 10% apnoeas occurring during resting expiration were excluded. *B* Electrodes. *B* for noise. *B* was prevented distortion of wave form and amplitude due to varying skin-electrode impedance contacts. *C* Time-code generator. A time-code signal was generated during the tape recording of all electrocardiographic data. The time code was used for editing purposes to localize data on tape for analog-to-digital conversion. *D* Amplification system. The high-gain AC amplifiers were part of an Ampco data acquisition system. *E* Tape recorder. Five channels of electrocardiographic information and the time code were recorded simultaneously. While the data were being tape recorded, the output of the tape recorder was fed to a graphic recorder (*F*) to determine that technically good data were being obtained. *G* Analog-to-digital converter. Once editing had been performed, the data on tape were transferred by an analog-to-digital converter to a digitizer rate of 256 samples per second per channel. *H* IBM 1802 digital computer. The digital tape were processed by the computer and the outputs all had were then used in reference to the base line (1 R segment) in every 100 second. *I* Computer output. The final output was programmed in a format suitable for the individual output shows 12 mm interval were printed out spatially to correspond in position to the individual lead placed on the body surface. After the maps were processed for the automatic construction of isopotential maps (*J*) by Calcomp plotter.

trocardiograms and vectorcardiograms (Frank system) were interpreted as being normal.

Introduction of isopotential maps

A. DATA ACQUISITION METHODS. A schematic representation of the data acquisition and processing system is shown in Fig. 1. All patients were studied in the supine position. To explore the entire thorax a grid system was marked over the upper abdomen and thorax to record

from 150 to 250 points (Fig. 2). The distance between the explored points was 2.5 to 3.0 cm over the anterior and lateral chest surface over the back the distance between the points was 2 to 3 cm vertically and 4 to 5 cm horizontally. The chest electrodes were gold plated brass plates 7 mm in diameter. Each electrode assembly consisted of a modification of the electrode developed by Dr. Loren Auger of the University of Tennessee

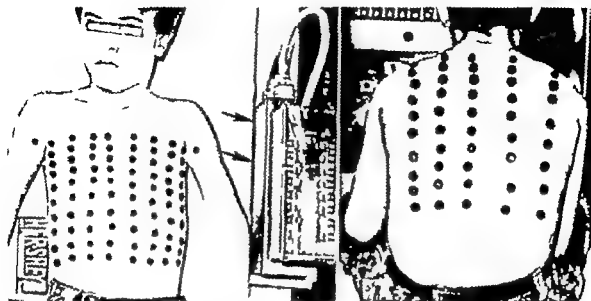


Fig. 2. (a) Diagram of electrode placement for recording, 150 points over the entire thorax. In the smaller children theopotential maps were constructed from 150 points. In children over 10 years of age 250 points were utilized. (b) The child made to feel at ease in the laboratory, a suitable point was used to construct the first lead as a point in the buffer unit which provided for impedance matching of the individual lead. (c) Note that the interelectrode distance is approximately twice as great for the back as for the anterior thorax. In calculating the average area for theopotential maps, the numbers for each point were weighted according to their area, the representation (see Appendix).

School of Medicine. A small layer of electrode cream (LH-501) was applied to each electrode. There was no cream outside each electrode border. To avoid skin electrode impedance variation producing loss of amplitude or distortion of the waveform of the tracings, the recording system included individual lead impedance matching and isolation through a buffer system.⁸ The buffer system contained a unity voltage gain input impedance amplifier between each electrode and the recording system input. These buffer amplifiers have an input impedance greater than 50,000,000 ohms and an output impedance of less than 10 ohms.

With the use of an Ampex Data Acquisition System 100, five tracings from the body surface were simultaneously recorded using a common left leg reference point. The technician held an array of five electrodes on an elastic band against the chest while a block of five points was recorded. After the block was recorded the procedure was repeated in a new position until all points were explored. Together

with each group of five tracings an additional time reference lead was recorded. This lead was chosen by placing an electrode on the thorax (referenced to the left leg) in a position so that the QRS complex produced a biphasic deflection. The entire procedure required approximately 2 hours. At the completion of the study, each patient was photographed and the lead placement for the Frank vectorcardiogram and conventional electrocardiogram was noted.

All data were recorded on magnetic tape. The entire system was found to have a frequency response flat to 5,000 cycles per second. The noise level varied from 0.015 to 0.05 millivolts (peak to peak) with the electrodes attached to the patient (Fig. 3). The seventh channel of the tape was utilized to record the output of a time code generator. While data were recorded on tape, the tape output was monitored by a Honeywell Visucorder 1503 oscillograph in order to edit the data for digital computer analysis. An impedance prometer was used to monitor

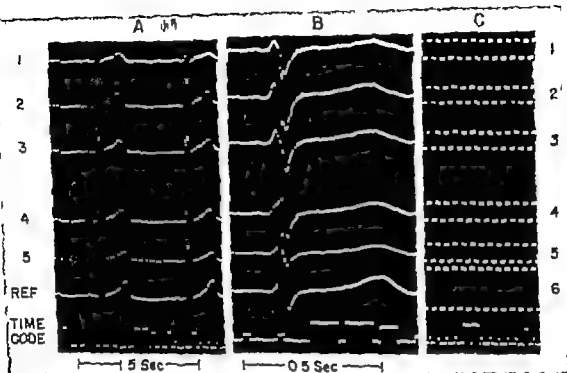


Fig. 3. Graphical readout obtained during recording of data. The upper five tracings represent recordings over the chest from five adjacent points while the reference lead was recorded simultaneously. The seventh channel of the tape recorded and reproduced the time-code signal which was utilized for editing and localizing on tape the reset complex to be processed by the analog-to-digital converter for computer analysis. Immediate visual inspection was possible by reproduction from tape of the complexes recorded at relatively slow paper speed (A). More rapid paper speed (B) were used to better detect noise and/or artefacts. Calibration of each lead is shown at C.

respiration only beats which occurred during resting expiration were analyzed.

DATA PROCESSING METHODS. The oscillographic data were reviewed and the proper beats chosen for analysis. By noting the complex to be analyzed in reference to the time code, the data then were processed automatically for input into an IBM 7072 computer. An Airborne Instrument Laboratories analog to digital converter sampling at a rate of 926 samples per second processed the data for input into the computer.

Through use of the wave identification program of Cuceres and co-workers¹⁰ the computer identified the QRS complex and defined the time line in the I R segment for the reference lead. The time of the time line crossing of the intracardiac deflection of the QRS was used for time localization. Voltage in all of the tracings were determined at 100 millisecond inter-

vals throughout QRS. Repeated checks of computer output indicated that time localization was accurate within ± 108 milliseconds. More rapid digitizing rates (e.g. 1852 samples per channel per second) produced no apparent change in the final isopotential maps.

Since the voltage at the left leg, varies throughout QRS, the zero voltage for each instant of time for the body surface was calculated from the total thoracic voltage distribution by averaging all measurements with appropriate weighting factors (see Appendix). The output was presented for 100 millisecond interval in a format which represented the thoracic distribution of the body surface voltage. Finally, another set of maps was automatically constructed by a Calcomp plotter (Fig. 4). From 60 to 110 isopotential maps were constructed for each subject.

II. Correlation of surface event with

surface as shown in Figs 5 and 6. Although there was variation in the distribution of isopotential lines among the subjects there was a consistent pattern which demonstrated six major events as follows:

1 The first indication of ventricular activation was the development of a relatively small maximum over the sternum anteriorly with a minimum at the left anterior axillary line or in the mid axilla (Fig. 7-8). The position of this early

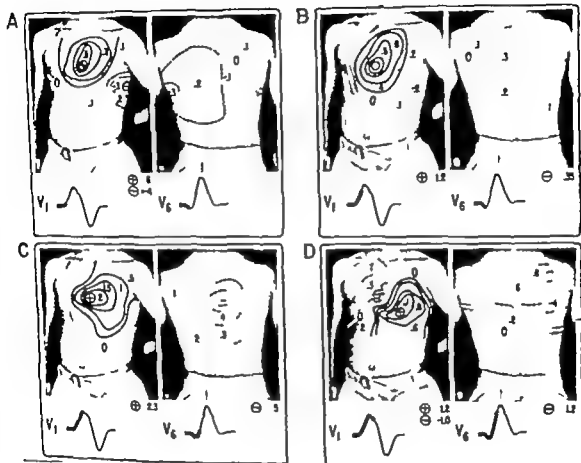


Fig. 5 Isopotential surface maps in a normal 8-year-old child. The sequence demonstrated of QRS is the transition of most of the children studied. It should be emphasized that many minor differences were found among the subjects of the normal group, however, the general pattern shown is consistent among the type studied. The white line indicates the calculated zero line; the solid lines denote positive and the dashed lines denote negative slopes. The + and - signs denote the highest (maximum) and lowest (minimum) isopotential areas respectively. 1 During the earliest stage of ventricular activation the distribution was dipolar with a small circumscribed maximum over the central anterior chest and the minimum located at the left axilla. This was associated with the onset of the R wave in Lead V and Q wave in Leads I, II, III, aVR, aVL, aVF, and the rise of the R wave in Lead V and the completion of the Q wave in Leads I, II, III, aVR, aVL, aVF, and the rise of the R wave associated with a rapid shift of the minimum to the central back. Thereafter the minimum increased with pseudopod extensions anteriorly down over the left precordium while the maximum remained in the central upper back. During the period of ST segment pseudopod extension occurred in the area of the maximum shown in C with the sudden emergence of discrete small minimum (-) over the central sternum with another maximum over the right shoulder. These two minima were regarded by some as reflecting greater voltage described by Tamarin (1954). During these events the maximum shifted inferiorly to the left and down over the left precordium. Direct right and left pseudopod extensions followed the development of the discrete minimum in the central sternum with the shift of the maximum to the right and down (Fig. 6).

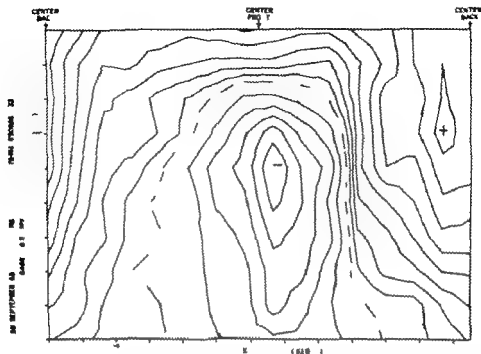


Fig. 4. Isopotential surface map produced by C-16 computer. The surface maps were calculated by the computer with a plotter. The isopotential lines are plotted on a grid. The date line indicates the calculated surface. The maximum (+) and minimum (-) are designated accordingly. The potential between the first map (0 mV) and the next (1 mV) is 0.1 mV for the positive box. The number in the box is the value of the potential. The printed and represented numbers designate positions on the isopotential map. The input program is designed to accept the plotter.

right ventricular epicardial activation sequence. Two patients with congenital aortic valvular stenosis and another with a ventricular septal defect underwent direct right ventricular activation studies at the time of cardiac surgery. Although these patients did not have normal hearts, the right ventricular pressures were normal and the isopotential surface maps through the first 30 milliseconds were similar to those obtained from normal children. Bipolar tracings were obtained from twenty areas over the right ventricular free wall. The recording electrode consisted of contacts spaced 2 mm apart. Lead II or III was recorded simultaneously as a time reference. The epicardial electrogram and LCC signals were amplified with Tektronix 122 preamplifiers recorded on an Ampex 51-300 tape system and later recorded on a Consolidated oscilloscope at a paper speed of 400 mm per second. For each tracing, the apex of the line crossing of the intrinsic deflection was used to determine the time of local activation at

each epicardial area. These points in turn were related in time to a sharp deflection point on the reference LCC. These data were used to construct maps of the sequence of epicardial excitation. Observations in these 3 patients provided a means for relating voltage changes at the body surface with the sequence of activation of the human right ventricle. The minimal timing error in relating events on the epicardial surface with the isopotential body surface maps was considered to be ± 2.5 milliseconds.

Results

In discussing the body surface voltage distribution, the terms employed by Lieberkühn will be used. A potential *maximum* is a region on the body surface where the voltage is higher than in the neighboring region. A potential *minimum* indicates a region where the potential is lower than in the surrounding region. Seventeen of the 70 children demonstrated a similar sequence of changing event on the body

3 The distribution changed rapidly with the minimum shifting in all children to the right scapula or upper mid back on the posterior surface with concomitant increasing negativity anteriorly over the right upper chest under the clavicle. Coincident with these events and immediately thereafter pseudopods enveloping negative voltage projected into the area of the mid sternum anteriorly. These pseudopods encroached upon the area surrounding the maximum either from the right upper chest or from a direct superior direction down inferiorly toward the central sternum.

The development of pseudopods occurred over an interval of 3 to 8 msec and was followed by the rapid emergence of another area of negativity in the central upper sternum (this area later became the principal minimum). At this instant of time (Fig 5D) the surface voltage distribution was nondipolar and was quite characteristic of the distribution described by Taccardi¹ in adults with two potential minima (central sternum and right shoulder) and a saddle encompassing an area of relatively higher voltage interposed between the two minima. During these changes the maximum shifted slightly to the left over the precordium from its original central location. These events correlated with inscription of the peak of the R wave in Lead V₁. The development of the two minima and saddle over the anterior chest occurred 20 to 28 msec from the onset of initial activity on the body surface.

4 There was considerable variation in the configuration of the isopotential maps describing the ensuing interval; however Fig 6E and F present characteristic changes which occurred during inscription of the intrinsincoid deflection in Lead V₁ and onset of the intrinsincoid deflection in Lead V₂. In all patients this period was characterized by gradual enlargement of the anteriorly located minimum. Together with the increasing magnitude and size of the anteriorly located minimum there was the development of pseudopods from the maximum in a leftward direction posteriorly to the upper or lower axilla. These events occurred over varying periods of time (7 to 21

msec). In one child two minima (one over the right lower chest and another over the left anterior axillary line) developed transiently. Ultimately the maximum shifted to the left axilla while the area surrounding the minimum enlarged to cover most of the anterior chest.

6 The remaining period of ventricular activation (17 to 30 msec) was similar in all but 3 subjects. The characteristic sequence is shown in Fig 6G and H. The minimum enlarged anteriorly while the maximum shifted to the central back. During the final 5 to 10 msec the anterior minimum fragmented and the maximum over the central back disappeared. In several of the children the separation of the end of ventricular activation from the onset of the ST segment was difficult because of the development of a small maximum (0.1 to 0.15 mv) over the mid left chest. The maximum persisted during the inscription of the ST segment and showed further enlargement with the development of the T wave.

In 2 subjects the posterior maximum was accompanied by an additional maximum located over the upper central sternum and a minimum over the lower sternum during the last 15 to 25 msec of ventricular depolarization (Fig 7A). In 1 patient there was an anterior centrally located maximum with two precordial minima one on either side of the maximum (Fig 7B).

Discussion

A Limitation of methods. Precise documentation of the contour lines of cardiac potentials over the body requires (1) accurate time localization within complexes recorded from multiple points at different times and (2) knowledge of the noise level present in the final digital computer output in order to determine what is a significant change in voltage.

Through the choice of a reference tracing which was biphasic in form timing between various points recorded at different times was within the limits of ± 1.08 msec in the final output. Two subjects were mapped twice in order to determine the reproducibility of the results. Each pair of outputs showed excellent agreement.

During the recording of multiple points

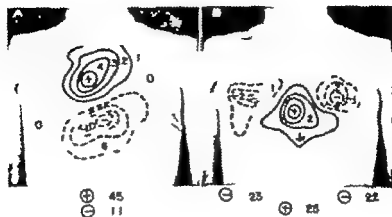


Fig. 7. Surface distribution of the QRS complex found in 3 children. A. In two children the surface distribution of the QRS complex was characterized by a maximum in the central back with an additional maximum over the upper central sternum (also in B). The minimum was located over the left lower pectoral region. B. In one child the surface distribution was characterized by a posterior maximum with the distally located anterior maximum with two minima situated on either side of the maximum. The surface distribution at the end of the QRS shown was suggestive of wave fronts located in the anterior-posterior and superior-inferior directions.

over the body individual electrodes occasionally demonstrated noise not present in the remainder of the tracings. This was especially true over the upper abdomen and right pectoral muscle. Such noise usually was muscle tremor and was eliminated by perseverance on the part of the investigator in working with the children by repeating tracings obtained from the same lead until technically good data were produced. Constant observation of the tape output while data were being accumulated provided visual checks to ensure a minimum noise level in the signals recorded data.

B. Potential information in isopotential maps. The isopotential maps in the children studied showed more nondipolar surface distribution than found in ECGs in adults. This may be related to the more frequent sampling of events, the enhanced proximity effects which are present in smaller subjects, or a boundary configuration which in children is different from that in adult.

The recorded surface maps showed a major event. On the basis of the work of several investigators⁴⁻⁷ the time course of these events was related corresponding events of ventricular excitation. Further, more several of these events were confirmed by direct measurements on the

surface of the right ventricle. The major events were the following:

1. The initial development of an anterior central maximum and left axilla minimum (Fig. 5A) was probably due to the predominant wave front invading the left septal surface.

2. During the following stage with the shift of the minimum posteriorly and enlargement of the maximum over the central sternum the contours of the body surface potential were predominantly dipolar in nature (Fig. 5B and C). This interval suggested invasion of the ventricular free walls with the major wave front becoming oriented in an inferior posterior direction.

3. Immediately following this the distribution became nondipolar with the minimum shifting to the right scapular and upper right chest anteriorly and with the invasion of precordials over the sternum inferiorly. The midaxillary region rapidly developed a minimum which was separated by a saddle from the right shoulder potentials (Fig. 5D). As suggested by ECGs,⁴ this most likely reflected sequential breakthrough of wave fronts in the right ventricular free wall. Direct evidence that such is true was obtained in 3 children undergoing cardiac surgery; however the relationship was found to be more complex than the simple

occurrence of epicardial breakthrough. These children with normal right ventricular pressures demonstrated a normal sequence of epicardial activation over the right ventricular free wall as found by Wallace and associates.¹² The earliest time of epicardial breakthrough in the 3 patients studied occurred 5 to 7 msec before the development of the discrete minimum over the mid sternal region. The initial development of pseudopodia which would later emerge as the discrete minimum correlated best in time with the breakthrough of activation in the right ventricular free wall. From measurements of the sequence of epicardial spread over the right ventricle it was estimated that an area of 10 to 20 square centimeters of epicardial breakthrough had developed when the discrete minimum emerged over the central sternum with its adjacent middle (Fig 5D).

4 The enlarging minimum over the upper anterior chest correlated with the epicardial wave front completing its spread over the right ventricle (Fig 6E).

5 The subsequent shift of the maximum from the left anterior precordium to the left axilla and back (Fig 6F and G) suggested epicardial breakthrough of wave fronts in the anterior left ventricle while depolarization continued over the left lateral and basal left ventricular free wall.

6 The final phase of ventricular depolarization (Fig 6H) was characterized in most children by an inferiorly located minimum with a maximum over the central back. This suggests continued activation in the posterior basal left ventricular free wall and septum. In 3 subjects this terminal phase was characterized by an additional minimum over the upper central chest with a pattern similar to that found by Tricardi in several adults.¹ The inferiorly located minimum in these subjects suggests late activation wave fronts in the upper anterior septum and/or crista supraventricularis.

Summary

A method is presented for the production of isopotential surface maps in children. After recording from 120 to 200 points over the body the data were processed for analysis by a digital computer with

the output of an instantaneous surface map for approximately every millisecond. The presence of dipolar and nondipolar distribution of body surface potentials varied throughout QRS however the children demonstrated considerably more of a nondipolar distribution than found by Tricardi in adults. Direct evidence was obtained relating the development of a central minimum over the sternum to epicardial breakthrough of wave fronts in the right ventricular free wall. These studies add emphasis to the need for the further accumulation of data in patients with normal and abnormal hearts to define the time course and location of electrical events on the body surface since important information is available in areas not sampled by conventional electrocardiographic lead systems.

Appendix

A method for deciding the zero line in isopotential surface maps

When measuring the distribution of chest potentials on the surface of the body there is considerable advantage in recording each of the potentials against a constant reference point. In particular if the potential at the reference point does not change from instant to instant then the line designated 0 mv on the map for 1 msec corresponds to the line marked 0 mv on the maps for all other instants. However if the potential at the reference point does change from instant to instant then the lines do not necessarily correspond.

If the heart consisted of a single dipole generator throughout the sequence of its activation it would in principle be easy to measure points on the chest against a constant reference. The reference point would be the center of the dipole i.e. inside the body torso. Since the heart is not a physical dipole (even though it produces some dipole like effects) and since the interior points are not accessible as reference points a practical reference point must be some point or a combination of points on the surface.

If the reference used is a single electrode on the surface the reference point's potential changes with time. As the heart activity moves toward the point

reference point become more positive and when the cardiac activity on the whole moves away from the reference point the reference point becomes relatively negative. On the other hand if the reference is the average of a widely separated combination of points then the reference is more nearly constant. One such combination is the Wilson central terminal. The average of the points of the central terminal provides a more nearly constant reference because when the potential of one rises the potential of another is likely to fall, thus the average remains about the same.

In order to facilitate the recording, construction and interpretation of topopotential maps at varying instants of time various reference systems were evaluated against these criteria: (1) convenience of recording and data processing; (2) applicability to surface maps previously recorded utilizing reference points at the left leg and Wilson central terminal; and (3) representation of the net electrical

effects of the heart at points on the surface by positive and negative areas of the potential distribution. Gelertner and Swihart¹⁴ have proposed a digital computer simulation scheme for evaluating the potentials produced on the surface of a volume conductor by internal current generators. Additionally, Selvester and co-workers¹⁵ have utilized digital computer techniques for simulation of the peripheral vector cardiogram. In this study the method of Barr and associates¹⁶ was used to estimate the zero line distribution utilizing four different reference methods. The purpose of the evaluation was not to add to the studies and theories of Bixley^{17,18} and Brody¹⁹ regarding zero lines but rather the purpose was to decide which of the proposed systems seemed both to give good answers in simulated problems and to be practical for surface map processing, while at the same time being a reasonable extension of related theoretical ideas.

With the use of an IBM 7072 computer three groups of dipoles were arranged

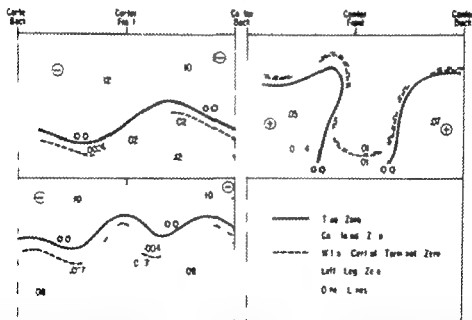


FIG. 2. Comparison of zero lines produced by different reference systems. The π surface distribution maps were derived by the method of Barr and associates¹⁶ utilizing a digital computer simulation program to arrange three groups of dipoles (each group containing approximately ten dipoles) in a cylindrical boundary. Each of the three maps shows the distribution of potential for one group. The distribution of the zero lines utilizing different reference systems is presented in comparison to true zero as produced by three internal generator configurations. Other lines represent isopotential lines of varying lines and distributed on the cylindrical boundary.

inside a cylindrical surface boundary. The computer calculated the surface potential distribution referenced to the dipole centers. Once the surface potential distribution was derived four isopotential lines were compared. The c represented the lines that would be called zero lines for references consisting of the dipoles center, the left leg, the Wilson central terminal and the average of all voltages.

Fig. 3 illustrates the results and shows the various lines that would be marked zero with the different reference systems used. The left and right edges of each map represent the center of the back of the cylinder. The true line is the zero potential referred to the dipoles centers. Note that the zero derived by averaging all voltages on the surface represents a close approximation of the true zero. The lines for the Wilson central terminal zero showed further separation from true zero whereas the left leg zero showed the greatest deviation of the methods evaluated. Notice that although the lines marked true are at approximately the same voltage on each map, the other lines are not. That is the true line has a consistent meaning with respect to the net generator activity in all three maps whereas the use of the left leg or Wilson central terminal reference system produced lines whose relationship to the net generator activity changed from map to map. In short by averaging the voltages over the walls of the cylinder giving equal areas equal weights a close approximation to true zero is achieved.

Since the foregoing results indicated that a close approximation of true zero could be obtained by averaging with proper weighting the values over the entire surface a similar program was designed for application to the isopotential maps recorded in patients. Originally the data were recorded with the left leg as reference. The main advantage of recording the thoracic potentials in reference to the left leg is that greater voltage values are recorded than when the Wilson central terminal is used. This affords a larger signal-to-noise ratio in the original data. The data is processed in the digital computer and instantaneous surface maps are derived. The numbers

are then weighted according to the area that they represent i.e. the anterior lateral thoracic points are weighted by a factor of 1 and those on the back are weighted by a factor of 2. (As shown in Fig. 2 the area sampled by each electrode on the back was approximately twice that of each point on the anterior lateral thoracic surface.) The average value derived is then designated as zero. Thereafter all of the points are recalculated the new value at a point is the old value minus the derived zero.

An additional advantage of producing isopotential maps in this method is that it allows the comparison of maps derived in various laboratories regardless of the zero reference point used. Since there is increased interest in this problem in many laboratories standardization of zero calculation may prove to be quite helpful in the future for uniformity of interpretation among different investigators.

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The relationship between the timing of atrial systole and the useful work of the left ventricle in man

Robert E. Snell MD*

Peter C. Luckstinger MD**

Cerald I. Shugoll MD***

Washington D C

The prominent phasic variations in arterial pressure noted in patients with an idioventricular cardiac rhythm have been related to alterations in the temporal relationship between atrial and ventricular contraction.¹ Presumably accompanying changes occur in the left ventricular volume output and in the useful stroke work. It has not been possible to quantitate these changes in man, however, with methods previously available.

The computed pressure gradient technique has recently been applied to the measurement of instantaneous blood flow in the human ascending aorta.² If aortic end-diastolic flow is assumed to be equal to the volume output of the left ventricle, can be estimated for individual beats. Such estimates, together with measurements of instantaneous aortic pressure, have been used to calculate left ventricular work and power in man under various conditions.³ The present report extends these observa-

tions to 3 subjects with required chronic complete heart block of unknown etiology. The patients were studied during idioventricular pacem, and the results were analyzed to determine the effect of variations in the timing of atrial systole on useful ventricular work and power.

Method

The patients were studied at rest with out premedication. All had required complete heart block and were judged to be suitable candidates for implantation of an artificial pacemaker. Prior to the actual operation, an electrode catheter was passed into the right ventricle and set to produce a stimulus rate near 60 beats per minute. The R-R and I-P intervals in each subject are shown in Table I. A specially designed dual lumen catheter was then introduced through the surgically exposed femoral artery and advanced to the ascending aorta just distal to the aortic valve

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From the Department of Medicine, University of Washington School of Medicine, Seattle, Washington.
*Present address: Department of Medicine, University of California, Los Angeles, California.
**Present address: Department of Medicine, University of California, Los Angeles, California.
***Present address: Department of Medicine, University of California, Los Angeles, California.
Reprint requests: Dr. Robert E. Snell, Department of Medicine, University of Washington School of Medicine, Seattle, Washington 98195.
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Measurements of instantaneous pressure, velocity and flow were then made as previously described.² In one patient the pacing frequency was increased and measurements were repeated at a second rate.

Recordings of pressure and velocity (flow) were displayed on a photographic recorder together with Lead II of an electrocardiogram at a paper speed of 200 mm per second. An average of 50 paired pressure and flow complexes were then selected at random for analysis in each subject. Ordinate values were measured at 1 mm intervals by a C-terber automatic scanner with punch card output. Left ventricular stroke work and power were then calculated from Equation 1³ using digital computation.

$$L.V.S.W. = \left(\int_0^t PQ dt + \int_0^t \frac{\rho Q v^2}{2g} dt \right) / 100 \quad (1)$$

where L.V.S.W. is left ventricular stroke work (cm M per beat), P is instantaneous aortic pressure (cm Hg), Q is instantaneous aortic blood flow (cc sec), v is instantaneous aortic blood velocity (cm sec), ρ is blood density (taken as 1.057 gm cc), g is the force of gravity (980 cm sec²) and t , t_1 is the systolic ejection period (sec). The factor cross-sectional area necessary to convert velocity to flow was obtained from measurements of the average vessel radius as determined by angiography.⁴

Values for pressure, stroke volume and stroke work in each subject were then grouped and averaged according to the associated I-R interval group. A consisted of beats with an interval between 0 and 0.09 sec and group B consisted of those with an interval between 0.10 and 0.19 sec etc. The seventh group consisted of beats with a I-R interval greater than 0.60 sec.

Results

The gross beat-to-beat changes in pressure, flow and stroke volume found in one patient are shown in Figs. 1 and 2. At a pacing rate of 60 beats per minute (Fig. 1)

Table I. I-R and I-P intervals in patients studied

Subject	I-R (yr)	I-R interval (sec)	I-P interval (sec)
53	69	1.010	0.680
63	63	1.005	0.590
81	53	1.005	0.600

there are variations in both peak and mean aortic pressure. The peak flow values remain relatively constant at this rate however and the changes in stroke volume (the area under the flow curve) result from beat to beat differences in the ejection time. At a rate of 105 beats per minute (Fig. 2) there are more prominent variations in both peak and mean pressure and flow.

Average mean systolic pressure, stroke volume and stroke work in each patient at rates near 60 beats per minute are shown in Table II and the relationship between the P-R interval and the useful work is illustrated in Fig. 3. Work maxima are seen in each subject in two when the interval is between 0.10 and 0.19 sec and in the third when it is between 0.20 and 0.29 sec. Beyond this optimum time pressure and stroke volume both diminish with work output decreasing an average of 20 per cent from the peak value. Further lengthening of the I-R interval however does not significantly alter the work done until the time exceeds 0.60 sec. At this limit when the atrial contraction would be expected to have occurred during the preceding ventricular systole a further drop in external work is seen in the two patients with the slower atrial rates.

The effect on this relationship of an increase in the pacing rate is shown in Fig. 4. Comparison with values for the same individual in Fig. 2 shows that the work done at any given I-R interval has diminished. Most striking at the higher rate is the almost 100 per cent drop in the work accomplished when the interval exceeds 0.30 sec and there is no effective atrial contraction during the preceding ventricular diastole.

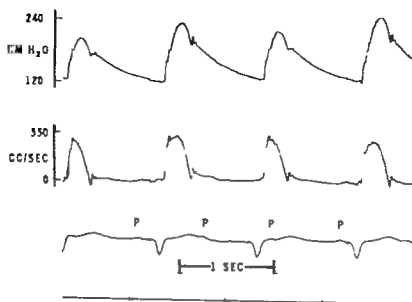


Fig. 1 Measurements of pressure, flow, and Lead II of an ECG made in one subject (No. 53) in the ascending aorta during transvenous cardiac pacing at a rate of 60 beats per minute.

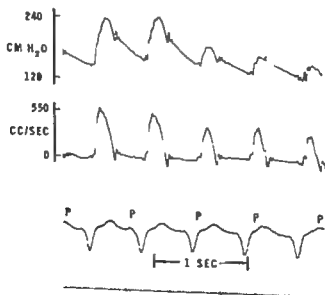


Fig. 2 Measurements as in the same individual as in Fig. 1 during pacing at a rate of 10 beats per minute.

The difference between two consecutive beats in the temporal pattern of work performance is shown in Fig. 5. During the early portions of the ejection period power output is about the same in both beats. At the shorter P-R interval, however, there is both a marked increase in values for instantaneous power output in late

systole and a prolongation of the ejection period resulting in a larger total work output.

Discussion

Many investigators using various experimental models have confirmed the importance of an appropriately timed

Table II Average stroke volume mean systolic pressure and stroke work at different P R intervals

		P R interval (sec)						
Age		0.10-0.19	0.20-0.29	0.30-0.39	0.40-0.49	0.50-0.59	>0.6	
54	SV	5	28	58	88	5	60	
	MSI	166	122	187	185	18	11	
	LVSW	82 ± 4	111 ± 3	10 ±	104 ± 7	107 ± 3	88 ± 5	
65	SV	0	28	5	6	16	17	
	MSI	1	1	78	1	13	13	
	LVSW	140 ± 2	151 ±	166 ±	145 ± 7	151 ± 2	147 ± 9	
81	SV	41	5	4	4	44	4	
	MSI	66	9	71	7	59	13	
	LVSW	112 ± 8	148 ± 2	111 ± 10	114 ± 11	114 ± 5	118 ± 8	

SV = stroke volume; MSI = mean systolic pressure; LVSW = stroke work. The values are the mean ± standard error of the mean. The values are the mean ± standard error of the mean. The values are the mean ± standard error of the mean.

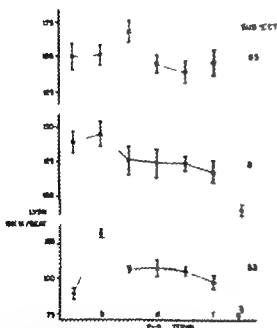


Fig. 1 Left atrial stroke work (SV) of the preceding P R interval in 3 subjects with complete heart block during tria. Each subject was paced at rate of 60 beats per minute. In each subject individual values for stroke work were first grouped according to the P-R interval as follows: Group a—P R interval 0.10-0.19 sec; b—0.20-0.29 sec; c—0.30-0.39 sec; d—0.40-0.49 sec; e—0.50-0.59 sec; f—>0.60 sec. The grouped values were then averaged for each patient. The vertical line represents the standard error of the mean.

atrial contraction to the subsequent ventricular systole.¹ "The extent of this atrial contribution is conditioned by the state of the myocardium and is more pronounced in individual with congenital heart block than in those with acquired disease." The results of the present study indicate that useful ventricular work may vary from beat to beat by as much as 100 per cent depending upon the presence of an atrial contraction, its placement in time and the cardiac rate. The actual variation are probably even greater since average vessel radius was used in determining blood flow in these studies and changes in aortic diameter were not taken into account.

Of interest is the finding that ventricular work does not fall off progressively as the interval between atrial and ventricular contraction lengthen. Once the optimal P R interval is exceeded the useful work output is not significantly lessened by a further lengthening of the interval as long as the atrial contraction falls within the diastolic filling period. When atrial contraction is simultaneous with the preceding ventricular systole, however, there is a further drop in the work accomplished. A possible explanation for this finding can be offered. It is known that left atrial contraction influences both ventricular filling

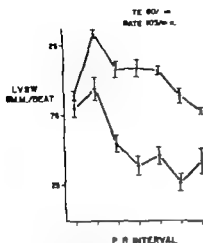


Fig. 4 Left ventricular stroke work as a function of the preceding P-R interval in one subject at two different pacing rates. Work values were grouped and averaged as in Fig. 3.

and mitral valve closure.^{1,2} Probably the occurrence of atrial systole in early ventricular diastole is relatively ineffective with regard to the former effect but still aids in valve closure and limits regurgitation. When atrial action is completely absent however both decreased filling and delayed valve closure could result in a further lessening of the useful work accomplished. Simultaneous measurements of left atrial pressure would be necessary to verify this.

One practical point arises from the

variations in stroke volume found at different P-R intervals. If the relationship between the P-P and P-R intervals is such that beats both with and without an atrial effect occur within short intervals of time repeated measurements of mean cardiac output at the same heart rate should be similar. However if the relationship between the intervals is such that a long series of beats with effective atrial contraction is followed by another series without an atrial effect determinations of mean flow would be highly dependent on the time of measurement. In judging the response of the heart to changes in idioventricular pacing rates this phenomenon would have to be taken into account.

The extent of the effect of atrial contraction is dependent on the heart rate as shown by the preceding results as well as by those of other investigators.¹⁰ This dependence presumably reflects the diminution in diastolic filling time at higher rates and the resulting increase in the importance of atrial contraction to ventricular filling.

Summary

Beat-to-beat variations of as much as 100 per cent in the external left ventricular stroke work have been found in 3 patients with acquired chronic complete heart block studied during idioventricular pacing. These changes in work output reflect the presence or absence of a preceding

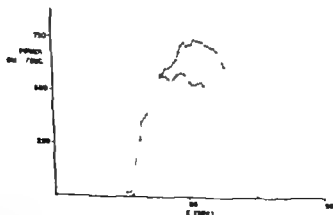


Fig. 5 In this case the output of the left ventricle in one subject during two beats at a pacing rate of 60 beats per minute. Zero time on the abscissa denotes the onset of the QRS deflection on the ECG. The interval preceding one beat (— curve) is 0.15 sec. that preceding the other (— curve) is 0.43 sec.

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The effect of quinidine on electrical energy required for ventricular defibrillation

Donald J Woolfolk MD*

William R Chaffee MD

Willard Cohen MD

John F Neville MD

J A Abildskor MD**

Syracuse N Y

The use of brief high voltage direct current pulses has been a significant advance in the therapy of cardiac arrhythmias¹ The rapidity and relative certainty with which some arrhythmias can be terminated by this means also facilitates evaluation of factors involved in the conversion of arrhythmias In the present study the effect of quinidine on the electrical energy required for ventricular defibrillation has been investigated Previous studies of the effect of quinidine on the ease with which defibrillation can be accomplished have given conflicting results^{2,3}

Materials and methods

Experiments were performed on 20 dogs in the weight range of 10 to 18 kilograms The animals were anesthetized with sodium pentobarbital 25 mg per kilogram and sodium barbital 400 mg per kilogram The latter long acting agent was used to provide a uniform level of anesthesia throughout each experiment and minimize

possible effects of this level on the energy necessary for defibrillation Tracheotomy was performed and the animals were artificially hyperventilated with a mixture of 95 per cent oxygen and 5 per cent carbon dioxide This had the object of fixing alveolar CO₂ at a level close to that in the inspired gas and maintaining stable PCO₂ and pH together with adequate oxygenation thus minimizing the possible effect of these items on the energy requirements for defibrillation

Ventricular fibrillation was induced by electrical stimulation at a rate of 40 c.p.s using a bipolar needle electrode inserted into the myocardium through the intact chest wall The onset of fibrillation was considered to be the moment of application of the stimulus and a D.C. shock of the energy level being tested was applied after 6 seconds of fibrillation If the test shock was unsuccessful defibrillation was accomplished with a higher energy shock to permit continuation of the experiment

* In the Department of Medicine, State University of New York at Syracuse, N. Y.
** In the Department of Medicine, State University of New York at Syracuse, N. Y.
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From the Department of Medicine, State University of New York at Syracuse, N. Y.
Reprint requests: Dr. Donald J. Woolfolk, Department of Medicine, State University of New York at Syracuse, N. Y. 13210.

A recovery period of at least 1 minute in normal sinus rhythm was allowed to elapse before ventricular fibrillation was reinduced. Three to five energy levels of DC shock were tested in each experiment and an effort was made to include one level which was usually successful and in intermediate level. Each energy level was tested ten times with individual application of the various levels carried out in rotation. The time required for the evaluation of energy necessary for defibrillation under a given set of conditions depended on the number of energy levels tested and the number of failure which had to be followed by a second shock of higher energy level. To make the experiment as uniform as possible, each evaluation of energy requirements under new conditions was made at 1 hour intervals.

Direct current shocks were furnished by a capacitor discharge type of defibrillator through circular electrodes 5 cm in diameter. The kinetic to which the electrodes were applied were prepared by shaving and the application of an abrasive conductive gel and electrodes were bound to sites on the right and left lateral chest walls.

The spontaneous variability of energy required for defibrillation under the conditions of the experiments was evaluated in 6 experiments. Fibrillation was repeatedly induced and terminated over a 3 hour period which was comparable to the time required in most of the experiments in which the effects of quinidine were evaluated. The effect of quinidine was studied in 11 experiments. One to three 200 mg dose of quinidine gluconate were administered intravenously in these experiments and a series of test shocks was applied beginning approximately 5 minutes after each dose.

Because of the known hypotensive effect of quinidine and the possible influence of blood pressure on energy required for defibrillation, femoral arterial pressure was recorded continuously in 3 experiments. After the administration of quinidine and the application of test shocks to define the energy required for defibrillation, angiotensin was infused with a variable speed pump and the infusion

rate was regulated to maintain monitored blood pressure at the level which existed prior to the administration of quinidine. In these 3 experiments a series of test shocks was then applied under the new condition.

Results

There was a variability in the energy required for defibrillation in different animals. This ranged from an occasional successful defibrillation with an energy level of 10 watt seconds in one animal to a level of 30 watt second for an even occasional defibrillation in another animal. Spontaneous variability of energy required for defibrillation was much less marked in the individual experiments in which this was investigated. An example of these results is shown in Fig. 1 and a summary of results in the 6 experiments in which spontaneous variability was observed is illustrated as part of Fig. 3. In the experiment illustrated in Fig. 1 ten applications of 20 watt second shocks resulted in one successful defibrillation at the beginning of the experiment, two successful defibrillations 1 hour later, and one defibrillation after 2 hours. Similar small variability in the number of successful defibrillations at energy level of 30 and 40 watt second is also shown.

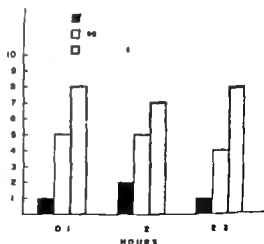


Fig. 1. Spontaneous variability of energy required for ventricular defibrillation in one experiment. The number of successful defibrillations achieved with 10 applications of each of the energy levels shown are indicated by the height of the bars.

Quinidine increased the electrical energy required for defibrillation. This is illustrated by the data from one experiment shown in Fig 2 and by Fig 3 which shows some of the data from all 11 experiments in which quinidine was administered. In the experiment the results of which are shown in Fig 2 shocks of 30 watt seconds resulted in successful defibrillation in 5 of 10 applications prior to the administration of quinidine. The observations made 1 hour later and beginning 5 minutes after the intravenous injection of 200 mg of quinidine showed no successful defibrillation with shocks of that energy level. There were likewise no successful defibrillations at this energy level after the administration of an additional 200 mg of quinidine. Shocks of 40 watt seconds successfully defibrillated the ventricles in 6 of 10 applications prior to the administration of quinidine and were never successful after 200 and 400 mg of quinidine had been given. Prior to the administration of quinidine 50 watt second shocks were uniformly successful in producing ventricular defibrillation. After 200 mg of quinidine this energy level achieved defibrillation in 3 of 10 applications and was successful in only 2 of 10 applications after a total dose of 400 mg of quinidine.

Fig 3 shows results from 17 experiments. The number of successful defibrillations with an energy level which usually resulted in defibrillation prior to the administration of quinidine is plotted on the ordinate. This energy level is thus not the same for all experiments illustrated. Time is represented on the abscissa. The data represented by dotted lines are from experiments in which no quinidine was given and show the small spontaneous variability in energy necessary to accomplish defibrillation. The solid lines indicate the effect of quinidine on energy levels necessary to defibrillate the ventricles. With one exception there were always fewer successful defibrillations with a given shock energy after the administration of quinidine and larger doses of quinidine increased this effect.

In the 3 experiments in which blood pressure was monitored there was a consistent fall followed by a gradual rise in

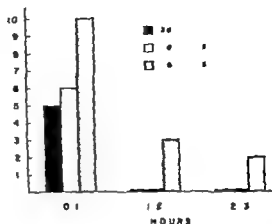


Fig 2 Energy requirements for ventricular defibrillation before the administration of quinidine and after 200 mg of quinidine 5 minutes before the observations shown for the 1.2 hour period and an additional 200 mg before the 2.3 hour observation.

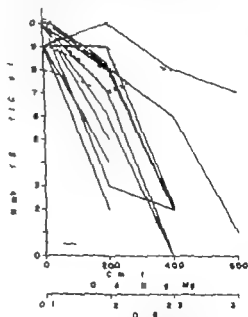


Fig 3 Data from 17 experiments showing the number of successful ventricular defibrillations achieved with 10 applications of electric shock. Data represented by dotted lines. Four experiments in which no quinidine was given and illustrate the small spontaneous variability of energy requirements for defibrillation under the conditions of these experiments. The solid lines show data from experiments in which quinidine was given in the amounts indicated and how the decreased number of successful conversions after this medication. The data shown represent different energy levels of the different experiments. An energy level which was therapeutically defibrillating in the actual observation is a criterion of the illustration.

pressure after the administration of either 200 or 400 mg of quinidine five minutes after quinidine had been given the series of trial shocks was begun. At that time the blood pressure level was lower than the control by amounts ranging from 21 to 49 mm Hg systolic and 31 to 48 mm Hg diastolic. When angiotensin was infused and the blood pressure levels were restored to control values the energy levels required for defibrillation were the same as those after quinidine alone. This suggests that the increased energy levels required for defibrillation after quinidine were the result of effects other than those on blood pressure.

Discussion

In this study quinidine increased the energy of D.C. shocks necessary to achieve ventricular defibrillation. Blood pressure levels were reduced by quinidine but the increased energy levels required for defibrillation were not altered by the restoration of control blood pressure levels with angiotensin. Spontaneous variations in the energy necessary for ventricular defibrillation occurred but were slight compared to those which followed the administration of quinidine.

The energy level required for ventricular defibrillation in this study were smaller than those which have been reported to be effective for this purpose.⁶ The reason for this difference is not certain but the short controlled duration of fibrillation and the measures employed to stabilize the respiration level, PCO_2 , and blood pH in these experiments may be involved.

The mechanism by which quinidine increased the energy required for ventricular defibrillation is not apparent from these experiments. The cardiac actions of this drug include decreasing the excitability and increasing the refractory period. The most likely effect of electric shock in terminating fibrillation is that of exciting all or most of the cardiac tissue at one time. This leaves all or most of the heart in a refractory state and blocks propagation of the irregular activation fronts which are probably present in fibrillation. Whatever the basic nature of the disorder decreased excitability after quinidine may reduce the mass of tissue which is acti-

vated and thus rendered inexcitable by electric shock. Quinidine is known to increase the threshold for the induction of fibrillation and this effect may also be the result of decreased excitability.⁷ Lengthening of the refractory period may have a similar effect in that some cardiac elements which might have been excited by a given shock had they been in a more advanced state of recovery are not activated when their refractory period has been prolonged by quinidine.

Results of this study indicate that higher energy level shocks are necessary to terminate ventricular fibrillation after the administration of quinidine. This may be of some significance in the clinical use of electric shock for ventricular defibrillation in that some patients with this dysrhythmia may have previously received quinidine for the control of other arrhythmias. The results should not be taken to indicate a similar effect of quinidine in atrial fibrillation. Quinidine has a vagolytic action which reduces the degree of dispersion of atrial refractory periods.⁸ If this effect existed alone it might enhance the likelihood of terminating fibrillation but it is complicated by the direct actions of quinidine on atrial muscle which include prolonging the refractory period and probably increasing the dispersion of refractory periods. The design of this study of ventricular fibrillation and quinidine would also be appropriate for the evaluation of factors which influence the energy requirements for atrial defibrillation and the effect of factors other than quinidine in ventricular fibrillation.

Summary

A technique for the evaluation of the electrical energy necessary for ventricular defibrillation under various controlled conditions was developed. Using this technique quinidine was found to strikingly increase the energy necessary for defibrillation.

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Observations on the effect of external counterpressure on the circulation through the forearm

B. I. Ardill M.Sc. M.B.

J. H. Lennett M.Sc. M.B.

London, England

The interpretation of measurement of blood flow in the forearm is complicated by the difficulty in separating the contribution of the skin circulation from that of the muscle circulation. Methods in current use for measuring blood flow in the skin and muscle compartments of the forearm are all subject to criticism.

Isotoplasma of adrenaline to abolish cutaneous blood flow¹ is effective only when a high concentration of adrenaline is retained in the skin. It is impossible to ensure that some of this adrenaline does not diffuse into the underlying muscle or enter the blood stream in sufficient quantities to exert central effects.

Attempts to deduce changes in blood flow from changes in the oxygen saturation of the effluent venous blood of the two forearm tissues depend on the assumptions that oxygen consumption remains constant and that the ratio of blood flow through nutrient and non-nutrient channel is unchanged.

Methods in which changes in the thermal conductivity of the tissues^{2,3} are used as an indication of changes in blood flow are at best only semiquantitative and like techniques which depend on the rate of clearance of a diffusible ion⁴ or radioactive

tracer are open to criticism on the grounds that they measure the blood flow through a very small sample of the tissue which may not be representative of the whole and which may have been disturbed by mechanical trauma due to the insertion of the tracer or probe. Recently Blum, Burnip and Lurie⁵ using the segmental plethysmograph technique noted a decrease in the measured blood flow through the forearm as the counterpressure in the instrument was raised. In a subsequent paper Blum and associates confirmed this finding using a capacitance plethysmograph with a pneumatic cuff inflated to various pressures situated under the sensors. They observed a progressive fall in measured blood flow as the counterpressure was raised from 7 to 2 mm Hg. With a further increase in counterpressure there was little change in blood flow until the counterpressure exceeded 5 mm Hg, when blood flow again declined with a further increase in counterpressure.

The flat portion in the curve between pressures of 2.5 and 3.5 mm Hg they took to represent a condition in which the skin capillaries were occluded because of the decrease in transmural pressure occasioned by the counterpressure where is the deeper

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muscle capillaries remained largely unaffected. Thus the recording of blood flow in the forearm with an appropriate counterpressure applied would give a measure of blood flow in muscular tissue only, whereas removal of counterpressure would allow the total blood flow in skin and muscle to be recorded in the usual manner.

In the light of the foregoing criticisms of other methods of separating blood flow in skin and muscle the claim that by means of this maneuver it is possible to obliterate the circulation in the skin of the forearm without modifying the flow in muscle merits careful scrutiny.

This paper describes a series of experiments designed to test this hypothesis using a water-filled plethysmograph suitably modified to enable various counterpressures to be applied to the forearm.

Methods

The subjects with one exception (see below) were normal healthy men varying in age between 19 and 39 years. All measurements were taken with the subject in the supine position and a rest period of 15 minutes was allowed to elapse before measurements were started.

Laboratory temperature varied in different experiments between 22° and 24°C but was held to within 1°C in any one experiment with the exception of heating experiments.

Blood flow in the forearm was measured by venous occlusion plethysmography using temperature-controlled water-filled plethysmographs.¹ The temperature of the water in the plethysmographs was maintained at $34 \pm 0.5^\circ\text{C}$. One instrument was modified as previously described by Hall² to permit measurements of blood flow in the forearm at different counterpressures between 10 and 0 cm H₂O. Particular attention was paid to the fit between the forearm and the hard rubber end pieces of the plethysmograph in order to prevent bulging of the soft tissue sleeves when the water pressure was raised.

Effect of pressure on flow. Twelve measurements of blood flow were taken in a period of 3 minutes at each of the following counterpressures in sequence: 10, 25, 40, 17, 32, 10, 27, 5, 30, 15, 35, 30, 10, 20, 4. The opposite forearm served as

a control and was exposed to a counterpressure of 15 cm H₂O throughout. To exclude the effects of the circulation in the hand cuffs were inflated at the wrists to a pressure of 200 mm Hg one minute before measurements were begun.³

A period of 1 minute was allowed to elapse after the counterpressure was applied before any measurements were taken. This was to allow equilibration of pressure throughout the tissues of the forearm. At every third change of counterpressure the wrist cuffs were released for 4 minutes and then the cycle was repeated.

Heating. The subjects were heated in messes of a cradle carrying six 1.0 watt tungsten filament bulbs located over the trunk. Oral temperature was recorded before and during the period of heating which was continued until the temperature had risen by about 0.5°C.

Groups of eight measurements of blood flow were made at each of two counterpressures, 10 and 45 cm H₂O in the experimental forearm before and every 15 to 20 minutes during heating. The lower counterpressure was chosen as that least likely to affect the circulation through the skin of the forearm. The higher pressure was chosen in the light of the results of Hyman and associates,⁴ the pressure most likely to occlude the circulation through the skin of the forearm in all subjects although we recognized that this pressure may also cause a diminution in the forearm muscle blood flow in some subjects.

Exercise. The experimental forearm was exercised by having the subject rhythmically squeeze with his hand a water-filled rubber bulb attached to a modified 0 ml record syringe approximately 0.1 mm in 2 minutes. Squeezing the bulb raised the plunger of the syringe which was watched with a 2.5 diopter magnifying glass. This degree of exercise was sufficient to fatigue the forearm muscles within the 2 minute period.

Eight measurements of blood flow in the forearm were taken at counterpressures of 10 and 45 cm H₂O before exercise in order to determine the resting flow. Immediately after the period of exercise 6 measurements of blood flow were made at a counterpressure of 45 cm H₂O followed by 6 measurements at a counterpressure of

10 cm H₂O. The pattern was then repeated until blood flow had almost returned to resting level.

The control forearm was exposed to a counterpressure of 1 cm H₂O throughout the period of exercise.

Skin temperature. Light measurements of blood flow were made in the experimental forearm and then the pressure in the plethysmograph was raised to 4 cm H₂O and maintained at that pressure for 4 minute. The pressure in the plethysmograph was then quickly dropped to 10 cm H₂O and blood flow was recorded for the next 3 minute. The opposite forearm served as a control being exposed to 1 cm H₂O throughout the experiment.

Results

Effect of increased counterpressure. The effect on blood flow in the forearm of 6 subjects of counterpressures between 10 and 50 cm H₂O is shown in the Appendix. Each figure is the mean of twelve measurements of flow and the standard deviation is also included. The corresponding mean blood flow in the opposite control forearm is also given together with the standard deviation.

The results in all 6 cases show a decline in blood flow with increasing counterpressure (see Fig. 1). In only 2 subjects (N 11 and 11 A) is there any evidence for a first portion in the curve. However when variations in flow in the control fore-

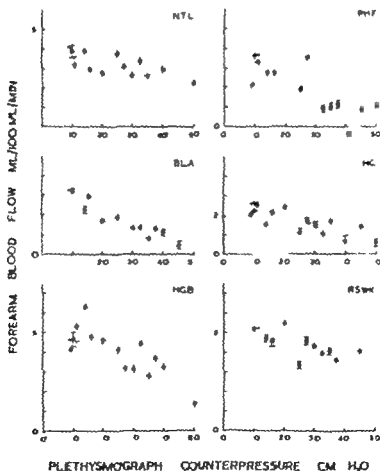


Fig. 1. The effect of counterpressure in the plethysmograph on forearm blood flow in 6 subjects. Mean of 12 (in the case of N 11 A) in blood flow measurements ± 1 standard deviation.

time is taken into account the significance of this becomes doubtful.

Heating. The results of the heating experiments are shown in Table I. Mean values for blood flow as measured at counterpressures of 10 and 45 cm H₂O both before heating commenced and at the end of the period of heating are tabulated together with the calculated difference in flow at the two counterpressures.

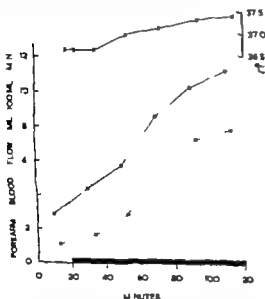


Fig. 1. Effect of body heating (0.9 kilowatt) on forearm blood flow in a normal subject. Each point is the mean of 8 individual flow measurements. Open dot curve: Forearm blood flow with counterpressure of 10 cm H₂O in plethysmograph. Solid dot curve: Forearm flow with counterpressure of 45 cm H₂O. X curve: Oral temperature.

In all cases heating caused a rise of at least 100 per cent in total blood flow in the forearm. However in only one individual was the increase in flow in tissues affected by a counterpressure of 45 cm H₂O greater than that in tissues unaffected by this counterpressure.

Fig. 2 shows the results obtained in one experiment (PHF). Here total blood flow was raised from 2.9 to 11.2 ml per 100 ml per minute in the experimental forearm during the period of heating. Exposure to a counterpressure of 45 cm H₂O lowered flow from 2.9 to 1.1 ml per 100 ml per minute before heating and from 11.2 to 7.8 ml per 100 ml per minute after heating. Results during the course of heating show comparable decreases when counterpressure was applied.

One of the subjects (H) was a patient who because of his height of 1.96 meters and weight of 30.8 kilograms had difficulty in maintaining his body temperature and during cold weather suffered from periods of hypothermia. He was chosen because the ratio of skin to muscle in the forearm would be higher than average and it was assumed that the contribution of the skin component to total flow in the forearm would be correspondingly greater.

The response of the forearm circulation to body heating in this case is shown in Fig. 3. It will be noted that the rise in total flow in the forearm in response to an increase of 1°C in oral temperature was modest but the blood flow recorded in tissues unaffected by a counterpressure of

Table I. The effect of body heating on blood flow in the forearm*

	Counterpressure (cm H ₂ O)	Subject				
		B.L.L.	PHF	R	C.V.	H.V.
Before heating	10	5.1	2.9	1.3	2.3	4.4
	45	2.6	1.1	0.6	0.5	2.1
	Difference	5	1.8	0	1.8	2.4
After heating	10	12.0	11	4.0	10.4	1.0
	45	9.0	7.8	1	1.7	7.9
	Difference	3.0	3.4	1.9	2	4.1

* Mean values for forearm blood flow at 10 and 45 cm H₂O together with the difference between the two values are given for each subject. The values for oral temperature are given in parentheses. The values for forearm blood flow are given in parentheses. The values for forearm blood flow are given in parentheses. The values for forearm blood flow are given in parentheses.

4 cm H₂O) were seen as a reflexion similar to that in the third subject.

The rate of the pattern of blood flow recorded in the post-exercise period was similar in all of 5 experiments in 4 subjects. Fig. 4 shows the results obtained in the 4

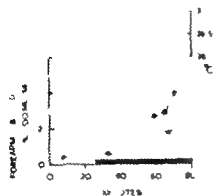


Fig. 3. Effect of rhythmic contraction of the forearm blood flow in the RLE group. The forearm blood flow was measured in the open and closed periods with a cuff pressure of 10 cm H₂O. The mean value of the forearm blood flow with a cuff pressure of 45 cm H₂O is shown as a horizontal line.

subjects. A repeat experiment on 1 of them gave a similar result. It will be seen that the flow through tissues affected by counterpressure varied during the postexercise period and at times accounted for up to 40 per cent of the total blood flow in the forearm. Blood flow in the control forearm was unchanged by the exercise.

Cutaneous reactive hyperemia. The pattern of the pattern of blood flow in the experimental and control forearm of 4 subjects in the period immediately after the reduction in counterpressure on the experimental forearm to 10 cm H₂O after exposure to a counterpressure of 45 cm H₂O for 4 minutes. It will be seen that reactive hyperemia was of an exceedingly small order.

Discussion

Of the two methods of application of counterpressure to the forearm segment, namely immersion of the forearm in water and the inflation of a pneumatic cuff on the forearm, the former might be expected to exert a more uniform pressure along the vertical diameter of the forearm, since the

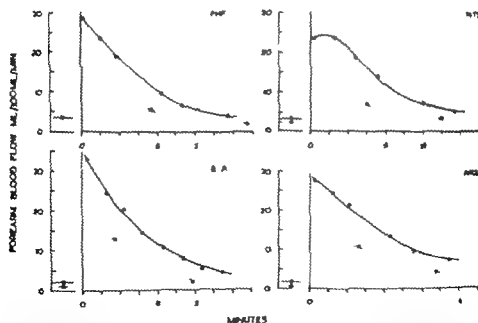


Fig. 4. Measurement of forearm blood flow in count per second of 10 ml 45 cm H₂O forearm and after a 2 minute period of rhythmic exercise of the forearm muscle. Each point shows the mean of 6 individual flow measurements. Open dot curve: Counterpressure of 10 cm H₂O. Solid dot curve: Counterpressure of 45 cm H₂O.

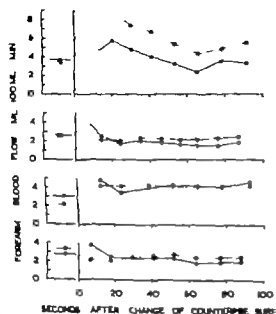


Fig. 5 Pattern of forearm blood flow in experimental and control forearm after exposure of experimental forearm to counterpressure of 45 cm H₂O for 40 min in the 4 subjects. Solid dot curve: Experimental forearm; counterpressure of 10 cm H₂O. Open dot curve: Control forearm; counterpressure of 15 cm H₂O. The point to the left of the critical line marking the end of the period of exposure to counterpressure are the mean of 8 flow measurements in the two forearms during the 2 minute period prior to exposure of the experimental forearm to counterpressure.

specific gravities of the forearm tissues and blood do not differ greatly from unity. Thus we consider that with our technique the change in transmural pressure is likely to be approximately uniform over the cross section of the forearm, provided that there is no interference with the transmission of pressure within the forearm tissues.

Hyman and associates⁸ suggest that a critical value of counterpressure must be exceeded before the pressure is transmitted to the deeper muscular tissues of the forearm, thus implying a barrier to transmission of pressure in the subcutaneous region of the forearm. Such a barrier would appear to be unlikely on anatomic ground because the antibrachial fascia and intermuscular septae are not structurally arranged to resist externally applied pressure. Furthermore, if this situation were to exist in the upper arm also, it would lead

to the arterial pressure being overestimated by between 25 and 35 mm Hg when measured by the auscultatory method.

The width of the pneumatic cuff is known to be of importance when measuring arterial blood pressure. In particular narrow cuffs tend to lead to overestimation of arterial pressure.¹ This is assumed to be due to the peculiarity of the pressure profile below the cuff which has been shown to be wedge shaped.¹²

In our experiments the length exposed to counterpressure was 1 cm, whereas Hyman and associates⁸ used a cuff 6.5 cm in width. Decreasing the length exposed to pressure would tend to decrease the volume of deep tissue experiencing increased pressure. Thomson and Doupe¹³ recorded a maximal tissue pressure of 89 per cent of the applied cuff pressure 3 cm in from the edge of the cuff at a depth of 3 cm in the forearm. At the same depth they did not achieve a reading of 100 per cent until the needle was more than 5 cm in from the edge of the cuff. They demonstrated a similar effect at depths less than 3 cm.

The results of Craf and Rosell¹⁴ support this hypothesis. They recorded a greater fall in forearm blood flow with increasing counterpressures in the range of 10 to 20 cm H₂O when they used two 5-cm segmental plethysmographs side by side on the forearm than with a single 5-cm plethysmograph. We would suggest therefore that the length of forearm segment exposed to counterpressure may well be critical.

One further criticism of the rationale of the technique is its implied assumption of a uniform pressure in small vessels in the forearm. With vasomotion the pressure in individual capillaries will be constantly changing and although the mean capillary pressure in a given volume of tissue may not alter under resting conditions there may well be a wide scatter of pressures around this mean value. Indeed the range recorded by Landis in 12 measurements of pressure at the arteriolar end of human capillaries was from 21 to 45 mm Hg, giving a mean of 32 mm Hg, the figure quoted by Hyman. Thus even if the counterpressure is applied evenly to the skin it is unlikely that a pressure sufficient

is correct imply that the conclusion supported by work using four different techniques that the increase in forearm blood flow during body heating is confined to the skin" is wrong.

The technique which we used to record postexercise hyperemia differed slightly from that used by H \ddot{u} man and associates⁶. In our experiments we recorded alternately at counterpressures of 10 and 45 cm H $_2$ O during the period of hyperemia following exercise. It might be argued that the rapid changes in counterpressure with almost immediate recording of blood flow would not allow sufficient time for equilibration to occur in the forearm circulation. However the experiments of Halperin and associates⁷ support our own finding that blood flow is stable after the equilibration of forearm volume at a new level—a process which is almost complete within 10 seconds of the change in counterpressure.

The results of the exercise experiments show that flow through tissues affected by counterpressure (presumed to be skin flow) was relatively high during the postexercise period at times exceeding 30 per cent of the total forearm blood flow. Furthermore this fraction varied considerably within the period of study.

Blood flow through skin overlying muscles which have been exercised may however rise during the postexercise period as is suggested by the recent work of Rolan and associates⁸ on the calf. They recorded a rise in the temperature of the skin of the calf and in the temperature of blood draining the skin of the calf during the postexercise period. Thus they interpreted as indicating an increase in blood flow in the skin during this period.

The mechanism of this inferred increase in blood flow in the skin has not been investigated. If however the increase is due to a direct heating effect of the underlying muscle mass one might expect the use of water-filled plethysmographs with a large heat capacity held at a constant temperature to minimize the effect.

In view of the variability and extent of the changes in postexercise flow in the forearm caused by counterpressure in the water-filled plethysmograph we conclude that with this apparatus the method does not provide a reliable means of separating

blood flow through muscle from that through skin under conditions of raised blood flow in muscle.

That reactive hyperemia occurs in the skin of the forearm is easily demonstrated by observing the changes in the temperature and color of the skin after a period of arrest of the circulation to the part. If exposure to counterpressures above 35 mm Hg causes arrest of the circulation in the skin it is reasonable to assume that exposure to 45 cm H $_2$ O counterpressure for a period of 45 minutes would result in some evidence of hyperemia.

The results of 4 experiments all show that the first flow after removal of counterpressure was elevated but the rise was in all cases very small. For comparison Patel and Burton⁹ recorded an initial flow of 65 ml per 100 ml per minute in the finger which can be regarded as representing mainly flow in skin after a period of arterial occlusion that lasted 7 minutes. This would imply that during the period of exposure to counterpressure the tissues of the forearm were experiencing a flow of blood adequate for their metabolic needs. Our finding is in keeping with the results of Dornhorst and Whelan¹⁰ who used a counterpressure of 67 cm H $_2$ O for much shorter periods.

It would appear therefore that although the application of counterpressure does lower the forearm flow and although the vessels situated near the surface of the forearm are more likely than deeper vessels to be affected by counterpressure factors other than site also influence the susceptibility of blood vessels to counterpressure. It is likely that a reduction in flow occurs preferentially in vessels which are already in a relative state of constriction. Furthermore the degree of localization of the effects of counterpressure to superficial tissues will be influenced by the length and diameter of the segment exposed to counterpressure.

We conclude that the selection of a suitable segment length for the counterpressure technique puts a serious limitation on its general use and that the application of counterpressure in the conventional water-filled plethysmograph does not provide a reliable method for distinguishing between the contribution of the muscle

Table 11. *Appendix*

		Counterpressure (mm Hg)					
		10	15	20	25	30	35
BFA	F per						
	M	4.16	3.8	3.5	3.1	2.8	2.71
	SD	0.33	0.43	0.39	0.5	0.20	0.40
	(n = 1)						
M	F per						
	M	4.05	3.83	3.40	3.45	3.15	3.6
	SD	0.53	0.46	0.3	0.36	0.31	0.5
	(n = 1)						
LHD	F per						
	M	1.9	3.62	3.3	3	1	0.5
	SD	0.31	0.53	0.33	0.57	0.36	0.40
	(n = 1)						
M	F per						
	M	3	3.58	3.8	3.61	3.81	3.42
	SD	0.45	0.8	0.4	0.35	0.5	0.11
	(n = 1)						
NLD	F per						
	M	4.43	3.8	3.15	3.33	2.99	3
	SD	0.43	0.3	0.35	0.35	0.44	0.43
	(n = 1)						
M	F per						
	M	3.3	3.13	3.35	3.8	3.71	3.94
	SD	0.42	0.43	0.3	0.30	0.17	0.39
	(n = 1)						
HCB	F per						
	M	4.27	4.6	5.11	6.44	4.6	4.61
	SD	0.45	0.31	0.4	0.36	0.42	0.3
	(n = 1)						
M	F per						
	M	3.33	3.06	3.36	6.16	4.06	4.05
	SD	0.3	0.3	0.6	0.63	0.4	0.5
	(n = 1)						
RWB	F per						
	M	3.61	3.30	4.81	4.23	4.55	5.60
	SD	0.18	0.27	0.57	0.33	0.31	0.1
	(n = 1)						
M	F per						
	M	4.53	5.7	4.54	5.9	4.55	4.85
	SD	0.36	0.5	0.43	0.41	0.36	0.13
	(n = 1)						
HIC	F per						
	M	0.5	2.26	3	1.5	2.15	4.5
	SD	0.31	0.38	0.90	0.45	0.28	0.25
	(n = 1)						
M	F per						
	M	3.33	3.15	3.19	3.14	3.8	3.20
	SD	0.68	0.30	0.54	0.50	0.25	0.35
	(n = 1)						

M = (8 sec 4 sec 30 sec).

and skin circulations to total blood flow in the forearm.

Summary

The effect of exposure of a 15 cm forearm segment to counterpressures in the range of 10 to 30 cm H₂O on forearm blood flow was measured in each of 6 subjects.

An increase in counterpressure resulted

in an approximately linear decrease in forearm blood flow. There was no consistent evidence for the existence of a range of counterpressure over which apparent blood flow remained constant.

Results of experiments in which forearm blood flow was measured at counterpressures of 10 and 45 cm H₂O during body heating, and during the period of elevated

experimental arm (cm H₂O)

25	77.5	30	37.5	35	37.5	40	45	50
1.94 0.39	1.58 0.47	1.39 0.47	1.39 0.34	0.84 0.32	1.32 0.32	1.16 0.16	0.45 0.19	0.66 0.29
4.85 0.22	3.87 0.39	4.06 0.33	4.86 0.34	3.87 0.34	5.11 0.35	6.37 0.57	3.83 0.17	4.18 0.84
1.99 0.84	3.51 0.54	1.23 0.22	0.99 0.12	1.03 0.19	1.15 0.21	0.99 0.31	0.96 0.30	1.13 0.79
3.50 0.10	4.61 0.51	4.09 0.15	3.54 0.28	4.30 0.50	3.18 0.38	3.36 0.18	4.63 0.44	5.91 1.07
3.78 0.17	3.08 0.31	2.62 0.33	3.38 0.60	2.63 0.24	3.03 0.25	2.94 0.3	7.10 0.71	21 0.34
4.09 0.25	3.85 0.78	3.77 0.4	4.52 0.19	3.82 0.39	4.65 0.18	4.08 0.45	4.08 0.50	3.95 0.41
4.14 0.31	3.17 0.37	3.14 0.39	4.48 0.68	2.78 0.33	3.71 0.49	3.24 0.40	— —	1.55 0.34
4.81 0.62	4.09 0.47	3.91 0.37	5.95 0.83	4.04 0.29	5.77 0.33	4.49 0.46	— —	4.01 0.56
3.35 0.16	4.65 0.15	4.33 0.44	3.94 0.30	4.10 0.19	3.63 0.21	2.20 0.30	4.10 0.37	3.26 0.15
5.58 0.11	5.68 0.16	4.91 0.18	5.71 0.24	4.83 0.24	5.86 0.27	6.41 0.67	4.58 0.28	5.18 0.4
1.13 0.2	1.6 0.20	1.53 0.13	1.06 0.36	1.71 0.35	0.93 0.41	0.69 0.74	1.43 0.29	0.63 0.18
8 0.27	3.17 0.16	1.0 0.77	2.98 0.83	3.54 0.42	3.47 0.52	7.95 0.47	2.9 0.31	3.70 0.37

Blood flow in the forearm after exercise of the forearm muscles did not demonstrate that exposure to a counterpressure of 45 cm H₂O in our apparatus caused up-pressure of blood flow through the skin of the forearm.

Exposure of the forearm segment to a counterpressure of 45 cm H₂O for 45 minutes did not result in reactive hyperemia

comparable to that induced in skin at other sites by period of arterial occlusion of much shorter duration.

Although it may be possible to suppress blood flow in skin without affecting blood flow in muscle by applying counterpressure to a short segment of forearm, our experiments indicate that it is not possible to do this in longer segments.

Appendix

Title II presents forearm blood flows (mean and standard deviation) for experimental forearm exposed to different counterpressures as shown and for control forearm exposed to a counterpressure of 15 mm Hg throughout for each of 6 subjects (figure 1). For ALL are the mean of 5 individual flows for all other subjects the mean of 10 individual flows.

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Endomyocardial biopsy

Experimental study with a catheter technique

James R. Hennemark MD*

Herbert V. Sommers MD

Ralph S. Zitrin MD**

Chicago Ill

Biopsy of the heart is in aid to diagnosis in endocardial and myocardial disease has been accomplished by various methods.¹⁻³ Some techniques require a thoracotomy which limits their application. Percutaneous methods have also been used but the hazard of cardiac tamponade or pulmonary complications during ventricular puncture is always present.⁴

Biopsy of the myocardium by means of an intravascular catheter technique would have obvious advantages. Multiple specimens could be obtained without the necessity of general anesthesia or thoracotomy. Cardiac tamponade or pulmonary complications would not be a problem. In 1967 Sakakibara and Honno introduced a bioprobe or biopsy catheter and subsequently reported its successful use in animals and human beings.^{5,6} More recently Bullock and associates⁷ have suggested another catheter biopsy technique for obtaining specimens of the ventricular septum from the right ventricle.

The present study was performed in dogs to determine the practicability and safety of the Honno intravascular biopsy catheter and the capability of this in-

strument to provide adequate samples for histologic and other studies.

Methods

Nineteen medium sized mongrel dogs were anesthetized with intravenous pentobarbital 15 to 30 mg per kilogram. A standard 12 lead electrocardiogram (ECG) was obtained at the beginning and end of each procedure. The right femoral artery was cannulated and pressures were obtained using a Statham P23A strain gauge manometer. Lead II of the ECG and the femoral arterial pressure were monitored throughout the procedure.

The right jugular vein and right carotid artery were exposed surgically. The bioprobe was first inserted into the right jugular vein and advanced into the right ventricle where in 18 dogs two separate biopsy specimens were obtained and where in 1 dog only one specimen was obtained. In 12 dogs the bioprobe was then inserted into the right carotid artery and advanced into the left ventricle where one biopsy specimen was obtained. All catheter manipulations were done under fluoroscopic control.

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After the initial four experiments the biopsy catheter was modified by adding a length of polyethylene No. 0 tubing along the side of the instrument. This is used to monitor blood pressure at the tip of the catheter and served as a conduit for the position of the biptome.

On removal of the biptome from the animal the specimen was carefully taken from the instrument gently flattened and unfolded. The endocardial surface was placed on a portion of stiff paper or light cardboard so that distortion inherent in taking the biopsy would not become a permanent part of the fixed tissue. The specimen was oriented and arranged on the paper splint and then placed in cold formalin (uff red to pH 7) with phosphate. All tissue were processed in the usual fashion and embedded in paraffin with sections cut at 5 microns. Sections were stained with hematoxylin and eosin by the Hudenham modification of the Mallory technique for connective tissue and in some instances by the periodic acid Schiff (PAS) technique with and without preceding diaphanization digestion. Elastic tissue stains were done using the Verhoeff technique with a 1 in 10 counterstain.

Two dogs were sacrificed immediately after biopsy, 2 others 24 hours later and 13 at time intervals varying from 12 to 21 days after biopsy. At the time of sacrifice the animal were again anesthetized with intravenous pentobarbital and the ECG was repeated. The heart was quickly excised weighed and opened along the interior wall of the inflow tract of the right ventricle and along the interior wall of the outflow tract of the left ventricle in order to locate the biopsy site. Tissues were taken for histologic study from all identified biopsy sites as well as from all abnormal appearing areas. All tissue specimens from the heart were processed in a fashion similar to the biopsy.

Results

Two animals developed complications. The coronary sinus was biopsied in one animal resulting in fatal tamponade. In the second animal the aortic valve was perforated resulting in severe aortic insufficiency.

After modification of the catheter to

include pressure monitoring, no serious complications were encountered. Frequent extrasystole were observed during the initial biopsy procedure. No significant change in the systemic blood pressure was seen at the time of biopsy. ECG's taken immediately after the procedure and at the time the animal were sacrificed did not show any significant change. All animals surviving the initial procedure were alive and appeared to be healthy at the time of sacrifice.

Sections of the biopsy specimens usually revealed a portion of myocardium and with careful embedding the endocardial surface could be identified. Multiple section production, a minimum of 10 to 15 slides could be cut from a single biopsy specimen. Hematoxylin and eosin stains proved to be best for the study of fine cellular detail (Fig. 1). Stains for connective tissue and elastic tissue were also satisfactory. Cellular morphology was well preserved although there was a tendency for the fibers near the edges of the biopsy material to separate and spread apart because of the lack of supporting connective tissue (Fig. 2). In many instances prominent contraction bands were present in myocardial fibers particularly those oriented near the edges of the biopsy specimen (Fig. 3). Although no precautions were taken to minimize the dissolving of glycogen within the fibers and no time performed with the specific end of identifying that substance moderate amounts of it were observed in specimens stained by the PAS technique. Lacking fibers were identified in biopsy specimens from the left ventricle. Little difference could be seen between biopsy specimens from the right and left ventricle with the possible exception that the endocardium was more easily identified in the specimens from the right ventricle.

Over half of the biopsy specimens taken from the right ventricle were obtained from the area near the junction of the interior wall of the right ventricle with the interventricular septum. Usually the biopsy site was located within that region which lies one half to two third of the distance between the base of the heart and the apex of the right ventricle. Biopsy scars in 3 dogs were found on the intern-



Fig 1 Endomyocardial junction from right ventricular biopsy. The normal relationship between the endocardium and myocardium is shown in this section. The detail of the endocardium and myocardial fibers is good. Sections of this type can be obtained with careful handling of the biopsy specimen prior to fixation. Hematoxylin and eosin stain (magnification $\times 130$).



Fig 2 Myocardial fibers from an area near the edge of biopsy specimen. Fibers have separated from each other because of a natural tendency to spread apart from lack of supporting connective tissue. Prominent contraction bands are seen throughout these fibers. In this tissue, contraction bands are most likely related to the trauma of taking the biopsy specimen. Hematoxylin and eosin stain (magnification $\times 350$).

medial wall of the right ventricle about midway between the tricuspid valve and the apex, and in 4 dogs scars were identified on the posteromedial wall of the right ventricle within 1.5 cm from the tricuspid valve.

In the left ventricle the most common site of the biopsy was midway between the posterior and anterior papillary muscles in that region which lies approximately one half to two thirds of the distance between the mitral ring and apex of the left



Fig. 3. On serial sections with toluidine blue, some of the large eosinophilic and partially hyaline particles are seen. In addition, there are many small, dark, circular structures, which are probably cellular debris. (toluidine blue, 100 \times magnification).



Fig. 4. Biopsy specimen 12 days after biopsy. The myocardial defect is filled with organized connective tissue and strands of collagen are extending radially from the biopsy site through the adjacent myocardial fibers. (Masson's trichrome, 100 \times magnification).

ventricle. In 3 dogs, biopsy scars were present medial to the posterior papillary muscle near the interventricular septum, whereas only 1 dog had a scar at the apex of the left ventricle. In 1 dog the biopsy scar was found high on the lateral wall of the left ventricle just beneath the mitral valve.

Examination of 2 dogs sacrificed immediately after biopsy of the right ventricle showed small hemorrhagic areas with beginning mural thrombi at the biopsy site. Two dogs sacrificed 24 hours after biopsy showed a focal inflammatory process in the myocardium associated with interstitial hemorrhage, segmented neutrophils and an overlying mural thrombus. By 12 days the defect showed a partially organized area with early collagen formation and by 21 days the biopsy site had been replaced by a well formed scar (Fig 4).

An unexpected finding in half of the dogs was the presence of an area of injury in the right atrium usually on the muscular limbus that separated the inferior and

superior vena cava. The injury was manifested by a fibrous plaque or partially organized mural thrombus. In most hearts sections showed the thrombus to have occurred over an intact endocardial surface with no evidence of myocardial damage (Fig 5) but in 1 dog, sacrificed at 24 hours a marked inflammatory reaction extended through the entire wall and was associated with focal necrosis of myocardial fibers. In one instance a mural thrombus was present on the anterior wall of the right atrium. The area of the limbus did not show any abnormalities. The dog with the largest mural thrombus in the right atrium also showed focal moderate to marked edematous changes in the tricuspid valve leaflets.

Discussion

The addition of a pressure monitoring channel to the biopsy catheter significantly improved the safety and ease of the procedure. Except for extrastokes during the biopsy, no other complications at the



Fig 5 Mural thrombus on wall of right atrium between the superior and inferior vena cava 17 days after biopsy. The nonseptal organized mural thrombus appears to involve only the surface of the endocardium. The endocardium is intact although the thrombus is most extensive. The thrombus was organized with only fibrous plaque remaining over the myocardium at the time of sacrifice. The injury in the right atrium is considered to be due to the trauma of introducing the biopsy catheter. Hemaphysin-Mallory connective tissue stain magnification $\times 9$.

time of the procedure were observed with the use of the modified catheter.

The biopptome itself is stiff and manipulation within the vascular system especially around curves is therefore difficult. This characteristic of the catheter undoubtedly account for the damage to the right atrium that was observed.

The construction of the catheter makes thorough cleaning of it difficult if not impossible.

The cutting tip of the biopptome is oval in shape. The catheter can be advanced and a bite taken in ventricular tissue but actual excision of the tissue is accomplished by crushing the myocardium between the jaws of the biopptome and withdrawal of the catheter with subsequent tearing of tissue rather than the making of a clean incision. The artifact induced by the crushing action of the biopptome can be minimized by the careful handling of the tissue before fixation but frayed fibers contraction band and other changes remain as a consequence of the method of taking the specimen.

The location of the biopsy sites and the speed of healing would indicate that the procedure would not under ordinary circumstances inflict a significant injury on the myocardium. The presence of the endocardial lesions in the right atrium would suggest that endocardial injury to sites other than that of biopsy can occur if the biopptome is used in its present form although it is possible that the likelihood of such injury would be less in man than in the dog.

A small sample of endomyocardial fragments of the right or left ventricle cannot be expected to give the same amount of information as may be gained from percutaneous biopsies of visceral organs. Diseases of the endomyocardium frequently have a residue of nonspecific fibrotic tissue which adds little in establishing the precise nature of the pathologic process.¹ Conversely the diagnosis of such conditions as glycogen

storage disease, endocardial fibroelastosis and myocardial disease might be considerably aided by endomyocardial biopsy. The role of myocardial biopsy in obtaining tissue for viral, biochemical and electron microscopic studies remain to be determined.

Conclusions

Biopsy of the endomyocardium has been experimentally evaluated in the dog using a biopsy catheter. The addition of a pressure monitoring channel to the catheter increased the safety of the procedure. An adequate amount of tissue was obtained for histologic and multiple histochemical studies and these may be of considerable help in determining the nature of some obscure cardiac diseases. Some endocardial injury to sites other than those biopsied was observed in the right atrium. This was most likely due to the design of the biopsy catheter used in this study which makes intravascular manipulation difficult.

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Case reports

Acceleration of the sinoatrial rate leading to complete heart block, an unusual mechanism for the Adams-Stokes syndrome

Paul L. McHenry, MD*

Suzanne L. Knoebel, MD
Indianapolis, Ind

The clinical picture associated with the Adams-Stokes syndrome when normal sinus rhythm prevails during symptom-free periods is in many ways distinct. Individuals with this phenomenon have been observed to have a very unstable functioning of the atrioventricular (AV) conduction system manifested by abrupt and transient episodes of complete heart block and ventricular asystole but some have also been free of Adams-Stokes attacks for long intervals of time.¹ The cardiac arrhythmias responsible for the syncope episodes may be missed because of a rapid return to normal sinus rhythm. The pathophysiology underlying such examples of unpredictable and episodic heart block as have been reported heretofore is uncertain but AV block as a result of increased vagal tone has been implicated in a number of cases.²

The present report concerns a case in which acceleration of the sinoatrial (SA) rate was documented as an unusual mechanism giving rise to complete heart block and ventricular asystole. Although an in-

crease in atrial rate has been postulated as a possible cause of intermittent complete AV block and Adams-Stokes attacks, such a mechanism has not to our knowledge been demonstrated clinically in man. The clinical course of this patient is otherwise quite typical of those individuals with the Adams-Stokes syndrome in whom normal sinus rhythm predominates between syncope episodes. Some of the difficulties which may arise in the diagnosis and management of such cases are demonstrated.

Case report

The patient, a 47-year-old woman, was admitted for the first time to the Indiana University Medical Center on Aug. 3, 1964, with the chief complaint of repeated blackout spells since February 1964. Previous to the episode she had been hospitalized briefly at her local hospital in May 1964. At that time the chest roentgenogram and routine laboratory studies were found to be normal and she was discharged without diagnosis, although a possible hypoglycemia was suspected. She seemed to have intermittent episodes of transient loss of consciousness until July 1964, when she perceived the onset of in-

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Reprint requests: Dr. Paul L. McHenry, Indiana University School of Medicine, 1136 E. 7th St., Indianapolis, Ind. 46202.
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interval has increased to 0.60 second (fifth strip)

Figure 2 is reproduced to confirm that sustained 1:1 A-V conduction was dependent upon the S-A rate remaining at 100 per minute or less. The two strips in each row are sections from one continuous tracing. In the top row the strip on the left shows a P interval of 0.16 second which shortens to 0.60 second in the right hand strip with the onset of complete A-V block. The bottom row shows a complete A-V block with an idioventricular rhythm and a P-P interval of 0.48 second. In the strip on the right the P-P interval gradually prolongs to 0.58 second at which time two I waves are conducted. When the P-P interval reaches 0.60 second sustained 1:1 conduction is again established.

Despite medical therapy the syncope attacks became more frequent and of longer duration. In an effort to prevent the attacks the patient underwent an operation for the implantation of a Medtronic artificial cardiac pacemaker. The pacemaker unit was implanted into the subcutaneous tissues of the anterior abdominal wall and the electrodes were attached to the epicardial surface of the left ventricle in the apical region. On the first post-operative day the ECG revealed a normal sinus rhythm and multiple pacemaker captures. The patient did well and she was discharged within 10 days. Two weeks after discharge she was readmitted because of a recurrence of symptoms of congestive heart failure. An ECG now revealed multiple pacemaker captures and frequent premature ventricular beats coupled to both the unit and pacemaker complexes. Daily administration for treatment of the congestive heart failure. On the evening of admission the patient suffered a Jacksonian seizure and a brief period of ventricular fibrillation was noted on the monitor but this reverted spontaneously to the previous rhythm. On the following day persistent ventricular fibrillation occurred and vigorous attempts to resuscitate the patient were of no avail.

Discussion

The sudden transitions from normal sinus rhythm to complete A-V block in this patient were unusual in that the underlying mechanism involved an acceleration of the S-A rate. Culchurst⁷ has emphasized the increase in block which occurs in second-degree A-V block Type II with acceleration of the atrial rate. However previous reports relating to the mechanisms underlying Adams Stokes attacks as a result of sudden transitions from a prevailing sinus rhythm to complete heart block have given more emphasis to the role of vagal influences upon A-V conduction.¹⁻⁴ There was evidence for considerable vagal effect upon the S-A node in the form of a sinus arrhythmia with P-P intervals as short as 0.48 second (lower left strip of Fig. 2) and as long as 0.76 second (upper left strip of Fig. 2). The A-V block was initiated however when the S-A rate was accelerating and the heart rate reached 100 per minute with a P-P interval of 0.60 second. The re-establishment of a sinus rhythm with a sustained 1:1 response was likewise dependent upon prolongation of the P-P interval to 0.60 second. The complete heart block in this case can best be explained on the basis of an abnormal prolongation of the refractory period of the A-V junctional tissues. When penetration

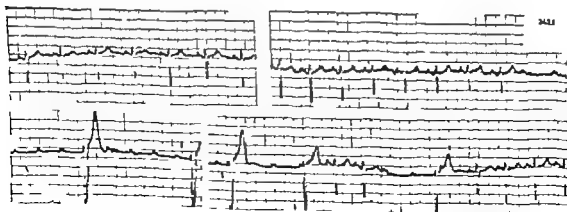


Fig. 2. Top row shows transition from sinus rhythm to complete A-V block. The bottom row shows complete A-V block with idioventricular rhythm and transition back to sinus rhythm. The P-P interval is 0.48 sec in the left strip and 0.58 sec in the right strip.

of the atrial impulse into the junctional tissues reached a rate of 100 per minute the maximal rate at which the AV junctional tissues could transmit impulse was exceeded.

Although reestablishment of a sustained 1:1 conduction was dependent upon a prolongation of the P-P interval to 0.60 second or greater it was also dependent upon the first P wave after an idioventricular complex falling within an R-P interval of 0.46 to 0.56 second. In fact as demonstrated in Figs. 1 and 2 one and at times two consecutive P waves were conducted at a time when the P-P interval was less than the apparent maximal rate of impulse transmission for the AV junctional tissue. One explanation for this phenomenon is that the P waves were conducted within the R-P interval because they arrived at the AV conduction system during the upnormal period set up by retrograde conduction of the idioventricular excitation wave.²¹ It is unlikely however that supernormality of the junctional tissues could account for the sustained 1:1 conduction when the P-P interval varied from 0.60 to 0.74 second. The more likely explanation for this unblocking effect of the idioventricular complexes was first described by Wolf¹² who reported a case of complete AV block in which isolated P waves falling within an R-P interval of 0.45 to 0.74 second after an idioventricular complex were conducted. Noting that the immediately preceding P wave fell within or just before the idioventricular complex he postulated that this P wave was blocked high in the AV node by concealed retrograde conduction of the idioventricular complex. This allowed for a longer recovery period for the AV conduction system resulting in conduction of the next P wave. In our case the 1:1 response was then sustained if the maximal rate of impulse transmission of the AV conduction system was no longer exceeded.

This patient gave a good history of an exacerbation of her syncope attacks after the administration of digitalis and the dangers of digitalis in this form of the Adams-Stokes syndrome have been emphasized.¹ It is also of interest to note that she had an increase in the frequency

and severity of the syncope episodes after the administration of Isuprel during her first hospitalization here. Schwartz and Schwartz¹¹ have pointed out that when normal sinus rhythm prevails during symptom-free intervals in patients with the Adams-Stokes syndrome the administration of sympathomimetic drugs may lead to an exacerbation of the episodes of heart block. If in this case Isuprel exerted an accelerating effect on the SA node without a proportional influence on AV conduction the tendency to AV block would be increased.

The surgical approach to therapy with pacemaker implantation was also unsatisfactory in this patient. The poor results obtained from pacemaker implantation in the presence of sinus rhythm have been emphasized by others.^{10,11} Although the mechanism initiating the terminal ventricular fibrillation was not recorded the induction of repetitive ventricular arrhythmias is a result of artificial pacemaker stimuli in the presence of incomplete AV block. It has been documented by Tavel and Fisch.⁸

Summary

Acceleration of the normal rate leading to complete heart block is reported as an unusual cause of the Adams-Stokes syndrome. It is postulated that the maximal rate of impulse transmission of the intraventricular conduction system was exceeded when the atrial rate reached 100 per minute and complete heart block resulted. The reestablishment of 1:1 AV conduction was dependent upon the atrial rate slowing to 100 per minute or less.

Many of the clinical features which tend to characterize individuals with the Adams-Stokes syndrome in whom normal sinus rhythm predominates between syncope attacks were evident in this patient. The diagnosis was delayed because of the transient nature of the syncope attacks and the cardiac arrhythmias responsible for them. Medical therapy once initiated failed to decrease the frequency or severity of the Adams-Stokes attacks. In fact there was the suggestion that Isuprel led to an exacerbation of the episodes of heart block presumably by increasing the atrial rate. The surgical implantation of an

artificial cardiac pacemaker was followed by the appearance of multiple ectopic ventricular premature beats and by ventricular fibrillation as a terminal event.

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Asymptomatic giant cell granulomatous myocarditis

Ward M O'Donnell M D

Richard H Mann M D

Lancaster Pa

Giant cell myocarditis is uncommon postmortem finding, with only 23 cases reported in the English literature. About half of the patients in whom the morphologic change was seen died suddenly and unexpectedly. The remainder followed a course of rapidly progressive refractory congestive heart failure associated with a high incidence of cardiac arrhythmias.

Giant cell myocarditis is a disease of unknown etiology and its differentiation from granulomatous myocarditis has been questioned. The relationship of this form of myocarditis to the structural alterations seen in syphilis, malarial, tuberculous, leishmanial myocarditis, actinomycosis, or protozoan disease is unsettled. The extracardiac involvement seen in some cases of giant cell myocarditis in which associated granulomas are found in the lungs and regional lymph nodes tends to remove this disease from the realm of isolated myocarditis. The striking observation of giant cells of either the Langerhans type or of myogenic origin in the fibrous granulomatous tissue separates this morphologic entity from the more common degenerative or inflammatory lesions of the myocardium. In fact it is unusual to have giant cell formation as part of the reparative process in any heart lesion other than in the known chronic infective granulomas.

Our interest in this problem was stimulated by a recent patient whose death was

attributed to his cardiac function but whose heart it autopsy showed the pathologic changes of giant cell granulomatous myocarditis. This patient never had symptoms which could be related to an underlying cardiac disease. The purpose of this report is to emphasize that giant cell myocarditis may exist in the absence of symptomatic heart disease, that the morphologic process may be preceded with death occurring from intercurrent disease, that the involvement of multiple organs can occur and that the pathologic changes can be seen in the elderly as well as in the young. Finally, the histopathologic changes in the kidneys in this case lend support for a hypersensitivity etiology.

Case report

A 76-year-old man was admitted to the General Hospital with a 10-day history of stomatopoech followed by aphasia, lack of comprehension and finally stupor. There had been a history of typical grand mal seizures for several years. The seizures were controlled by Dilantin. There was no history of head injury. The patient was known to have been diabetic for 5 years and was controlled by diet and Orinase.

A history was obtained of intermittent nagging pain in the joint covering a 50-year period and associated with periods of red painful swollen joints. Movement of the knees and ankles had been limited. The clinical picture was that of gouty arthritis and blood uric acid levels up to 10.3 mg per cent had been recorded. The only treatment needed was aspirin. There was no history of exertional dyspnea, chest pain or hypertension.

lar to the findings on a previous chest x-ray examination performed 5 years before.

The patient was given intravenous glucose with an 11% coverage antibiotics and intramuscular Dilantin. Despite fluid and adequate renal output the blood urea nitrogen rose rapidly to 210 mg per cent. The temperature returned to normal on the day after admission. The pulse rate remained in the range of 80 per minute and was regular. The blood pressure varied from 140/78 to 120/70 mm Hg throughout his stay in the hospital. The course in the hospital was one of progressive deterioration with rapidly developing azotemia. The patient died on the seventh hospital day.

Autopsy findings. The body was that of a well nourished and well-developed 76-year-old white man. The body length was 172 cm and the weight was estimated to be 185 pounds. Severe dermatitis was present in the lower extremities particularly in the ankle region. Pressure sores and cutaneous ulcerations were seen in the dependent portions of the body.

The heart weighed 330 gram and the left ventricular wall was 1 cm in thickness. The myocardium was brown with focal replacement by several pale yellowish gray areas in the left ventricular wall. Mild fibrous thickening of the mitral and aortic leaflet was observed. Both lungs together weighed 1120 grams and the parenchyma was reddish-gray and of increased consistency. The parietal and visceral layers of the pleura were adherent on the right side. The spleen weighed 400 gram and had late fibrous plaques in the capsule. The liver weighed 1500 grams. When the wall was opened there was a subdural hematoma as found on the left side. Moderate presore atrophy of the left cerebral hemisphere of the brain was noted.

The histopathologic study was most revealing particularly in the material from the heart. Multiple sections from the heart showed focal replacement of muscle by granulation tissue. The granulation tissue was of the type usually seen in the protracted course of a chronic infective granuloma. Fibrous tissue containing many lymphocytes and a small number of monocytes, plasma cells and eosinophils. The striking feature in these lesions was the presence of many multinucleated giant cells of the Langhans type. Some of these giant cells in which the cytoplasm lacked asterose Schumann bodies or inclusions. The inflammatory tissue was seen in the form of nodules replacing myocardial fibers and forming an interstitial pattern with varying heart fibers at the periphery. The epicardium was uninvolved but underwent inflammatory and fibrous changes. The aortic intima was slightly thickened because of fibrosis and infiltrations of polymorphonuclear leukocytes, lymphocytes and plasma cells were seen in the intima. Giant cells were not observed in the aorta. The proximal portions of the thoracic aorta contained heavy aggregation of lymphocytes and plasma cells in the adventitia. In the lungs there were granulomatous nodules showing fibrosis, plasma cells and lymphocytes in addition to a small number of the Langhans type. The remainder of the parenchyma small nodules containing plasma cells and lymphocytes were

observed in the alveolar walls. Acid fast and periodic acid Schiff stains of heart and lung tissue were negative.

The left kidney weighed 330 grams and the right 200 grams. The parenchyma was swollen and soft with reduced corticomedullary demarcation. Microscopically a heavy diffuse interstitial inflammatory exudate was observed mainly in the cortex. The infiltrate consisted of lymphocytes, plasma cells and some eosinophils. A few polymorphonuclear leukocytes were seen in some of the distal tubules.

Initial pathologic diagnoses included old left sided subdural hematoma, moderate presore atrophy of the left cerebral hemisphere, chronic giant cell granulomatous nodules involving heart and lungs, moderate concentric hypertrophy of the left ventricle of the heart, chronic fibrous pleuritis on the right side, moderately advanced generalized arteriosclerosis and acute interstitial nephritis.

Comment

Chronic giant cell granulomatous myocarditis is a rare disease and only 2 of 23 recorded cases were seen by the same investigators; the remaining 21 instances were individual case presentations. The infrequency of the lesion accounts in part for its obscure etiology and our lack of understanding of its pathogenesis. This granulomatous process must be considered to be a systemic disease since 10 of the 23 cases described involved extracardiac sites: lungs, aorta, tonsils and Fallopian tubes.¹ It is by no means an isolated myocarditis. In our patient the granulomatous change was seen in the lungs in addition to the heart.

This disease is seen in relatively young people; the median age of listed cases was 34 years. It has been reported in a 6-month old baby.² Our patient (76 years) is the oldest individual reported to have this condition; only one other case occurred beyond the fifth decade.

Although our patient had the morphologic changes seen in giant cell granulomatous myocarditis, he died from unrelated disease: massive subdural hematoma and a rapidly progressive renal insufficiency. He had no symptoms which could be related to his cardiac pathology. The lack of symptoms is not unusual since in half of the recorded cases there was sudden death without previous warning. It is probable that the heart muscle was involved by the granulomatous process to a lesser degree in our case than in those previously reported in the literature. If our patient

had not died from intercurrent disease there might have been a critical progressive destruction of myocardial tissue resulting in cardiac disability. He would then have been subject to sudden death or fatal rapidly developing congestive failure. It is also probable that the inapparent heart lesions existed for some time since the pathologic changes were those usually associated with protracted inflammation. In the cases reviewed in the literature, the structural changes were in keeping with a chronic inflammatory disease state. Cardiac dysfunction apparently is related to the degree and location of myocardial damage, but our patient demonstrated that giant cell myocarditis may exist for some time before the terminal catastrophic illness.

No specific etiologic agent has been incriminated in the pathogenesis of giant cell myocarditis. Rul and others¹ consider the morphologic change to represent a host tissue reaction to any one of several possible agents. *Mycobacterium tuberculosis*, leprosy, syphilis, fungi, protozoa, or helminths. To date parasites, tubercle bacilli, or known fungi have not been identified in the tissues by special staining methods. We suspect that microbiologic cultural studies have been inadequate since this rare disease is usually diagnosed after microscopic study. Collins also viewed the anatomic changes as representing a deep seated fungus infection or a hypersensitivity state.

Our patient had a rapidly developing azotemia which can be accounted for by the interstitial inflammatory change in the kidneys. Acute diffuse interstitial nephritis has been regarded generally as a complication of systemic septic states of bacterial or viral origin. It has also been related to hypersensitivity or allergic reactions to sulfonamides. Federer and Rosenblatt² have described granulomatous interstitial nephritis characterized by giant cells, mononuclear cells, eosinophils, and polymorphonuclear leukocytes in the interstitial areas of the kidneys as an allergic response to sulfonamides. Although the infiltrate in the interstitium in the kidneys of our patient did not contain giant cells, there was a cellular exudate consisting of lymphocytes, plasma cells, eosinophils, and polymorphonuclear leukocytes. We ascribe

these renal changes to a possible hypersensitivity reaction and think that this mechanism might also be responsible for the pathogenesis of the granulomatous lesions seen in the heart and lungs. This opinion would support Collins¹ who suggested the possibility of a hypersensitivity reaction on the basis of observed morphologic lesions in his reported case and Palmer and Michael³ who considered the same causal relationship because of the giant cell interitis observed in the myocardium in their patient.

A similar observation relating to a hypersensitivity etiology should be mentioned in reference to a case of granulomatous giant cell myocarditis which was reported from the Massachusetts General Hospital. It concerned a patient who had received oral penicillin therapy and developed a serum sickness type of reaction and an exfoliative dermatitis which suggested a hypersensitivity reaction. In the treatment of the dermatitis over a period of 3 months, the patient received steroids in dosage which were sufficient to produce a Cushingoid appearance at the time of his final illness. A rapidly developing, progressive congestive heart failure with tachycardia. The necropsy showed the changes of giant cell granulomatous myocarditis with a total lack of tissue repair. Either this was not a hypersensitivity reaction with respect to the pathogenesis of the myocarditis or the steroids were incapable of reversing the process. However from a therapeutic viewpoint if this entity is suspected it seems to be rational that treatment should include the use of large dosages of steroids. This seems to be especially true because of the catastrophic course of the disease.

Summary

A 76-year old man who was known to be an epileptic died from a massive subdural hematoma and a rapidly progressive renal insufficiency. Incidental findings at necropsy were the histopathologic changes of giant cell granulomatous myocarditis and granulomatous nodules in the lung. The patient had never had symptoms relating to his underlying cardiac pathology. It is postulated that the degree of myocardial involvement was not extensive enough to

interfere with cardiac function and in intercurrent viral episode precluded the usual progression of this disease. Chronic giant cell granulomatous myocarditis is part of a systemic disease of unknown etiology. However the renal lesions of acute interstitial nephritis seen in our patient lend support for a hypersensitivity mechanism. We think that this is the oldest patient to be reported on and the only one in whom the cardiac pathology was not the cause of death.

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Treatment of hypertension with antihypertensive diuretic drugs

Robert I Wolf MD*

Milton Mendlowitz MD

Julia Robo BS

Stanley I Cullow MD

New York NY

Several categories of diuretics have been employed for the treatment of hypertensive disease. They are (1) the mercurial diuretics (2) the benzothiadiazine and phthalimidine diuretics (3) the carbonic anhydrase inhibitors (4) the aldosterone antagonists and (5) the unsaturated ketone derivatives of the urea cycle (phenylacetate) and diuretics. These therapeutic agents which increase the renal excretion of salt and water represent highly significant achievements in medical pharmacology in recent years. Furthermore the mechanisms involved in the renal transport of water and electrolytes have been clarified by investigations of the mode of action of these drugs.

Over 50 years ago Ambard and Beaujeu¹ first recognized the importance of the dietary restriction of salt in the treatment of hypertension. Since that time it has been generally accepted that a reduction in the dietary intake of salt is important in the therapy of hypertensive disease. Although Ambard and Beaujeu¹ incriminated dietary chloride in the pathogenesis of hypertension it was Collip² and

colleagues who attributed the hypotensive effectiveness of the dietary restriction of salt to the dietary restriction of sodium and implicated the importance of the low intake of sodium of the Kempner rice diet in reducing the blood pressure.³

In spite of the fact that rigid restriction of the oral intake of sodium does reduce the blood pressure the inability of patients to accept this therapeutic regimen has resulted in its virtual abandonment. As early as 1945 it was reported that mercurial diuretics have a hypotensive effect⁴ but it was not until the benzothiadiazine diuretics were introduced in subsequent years that antihypertensive therapy with diuretic agents became recognized.

In order to understand the effects of the hypotensive diuretics on the kidneys it is necessary to appreciate the physiologic mechanisms involved in the renal excretion of salt and water. Three mechanisms of reabsorption of sodium by the kidney exist (1) sodium chloride transport (2) sodium for hydrogen exchange and (3) sodium for potassium exchange.

Sodium chloride transport Sodium is

* From U. S. Military Postgraduate School of Tropical and Hygiene, College of Medicine and (1) and (2) Meyer D. Hartman School of Tropical Medicine and Hygiene, New York, N. Y.

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Address reprint requests to Dr. Robert I. Wolf, 111 Fifth Avenue, New York, N. Y. 10003.

reabsorbed against an electrochemical gradient in both the proximal and distal regions of the nephron including the distal convolutions and collecting ducts.¹ Reabsorption of chloride follows passively. Reabsorption of sodium chloride in the proximal segment of the renal tubule quantitatively exceeds that occurring in the distal segment. An osmotically equivalent quantity of water is reabsorbed in the proximal segment of the renal tubule and reduces the volume of the glomerular filtrate by approximately 80 per cent. The ascending limb of the loop of Henle is relatively impermeable to water thereby resulting in a significant concentration gradient between the hypotonic fluid remaining in the lumen of the renal tubule and the medullary interstitial fluid.

Sodium for hydrogen exchange. Sodium for hydrogen exchange also occurs throughout the entire course of the renal tubule. Renal tubular cellular carbonic anhydrase enhances the reaction of CO₂ and water to produce carbonic acid which rapidly dissociates to yield hydrogen ion and bicarbonate. Hydrogen ion is exchanged for renal tubular lumen sodium which is returned with the bicarbonate to the extracellular fluid.

Sodium for potassium exchange. Sodium for potassium exchange occurs in the distal segments of the renal tubule after the sodium for hydrogen exchange has been virtually finished.^{2,3} The exchange of sodium for potassium is the principal method for the excretion of potassium. The adrenal cortical hormones particularly aldosterone regulate this process which is dependent upon the availability of sodium in the distal segments of the lumen of the renal tubule.

Mechanisms of water reabsorption by the kidney. An important feature of the renal regulation of water balance is the counter current multiplier and exchange system. This system allows the formation of high concentrations of solute in the interstitium of the renal medulla.^{4,5}

During hydropenia the osmolality of the proximal tubular fluid is isoosmotic with plasma renal tubular fluid at the bend of the loop of Henle is hypertonic and the renal tubular fluid in the first portion of the distal convolution is hypo-

tonic and becomes isotonic as it proceeds down this segment of the renal tubule. Antidiuretic hormone secreted during hydropenia increases the permeability of the distal convolution and collecting duct to water. Renal interstitial hyperosmolality permits reabsorption of water from the distal convolution and collecting duct thereby resulting in hypertonic urine.

During water diuresis renal tubular fluid entering the first portion of the distal convolution is hypotonic. In the absence of antidiuretic hormone the distal segments of the renal tubule are impermeable to water and the renal tubular fluid remains hypotonic. It is important to remember that the renal tubular fluid in the first portion of the distal convolution has a constant osmolality, therefore the total quantity of solute reaching this site governs the total quantity of water delivered to the distal convolution.

Mercurial diuretics. The mercurial diuretics produce natriuresis proximal renal tubular sodium reabsorption is inhibited and chloride reabsorption which follows passively is also inhibited thereby resulting in natriuresis and chloruresis. The urinary excretion of chloride may exceed the urinary excretion of sodium as a result of the sodium for hydrogen and sodium for potassium exchanges thereby resulting in hypochloremic alkalosis. Inhibition of proximal renal tubular sodium reabsorption results in the presentation of a large quantity of water and solute to the distal renal tubular segments thereby resulting in an increase in free water clearance. The excretion of potassium may be increased after the administration of mercurial diuretics in congestive heart failure by an enhancement of the quantity of sodium delivered to the sodium for potassium exchange renal tubular sites.

Although parenteral mercurial diuretic therapy does reduce the blood pressure the need for frequent injections makes this form of treatment impractical. The oral mercurial diuretics are less potent than the parenteral compounds. Drug idiosyncrasy, gingivitis and gastrointestinal distress are not infrequently observed side effects.

Benzothiadiazine and phthalimidine diuretics. The benzothiadiazine diuretics have

distal renal tubular salt reabsorption. During m_k water diuresis they reduce the rate of formation of solute-free water. They do not inhibit the production of a maximally concentrated urine and do not decrease the reabsorption of solute-free water during m_k hydropnia. This evidence suggests that these compound have their predominant action in the distal convoluted tubule.

During the past several years the structure of chlorothiazide has been altered yielding many congeners which comprise the thiazide diuretic group. All of these thiazide diuretics may be used interchangeably. When employed in maximum dosage they have equivalent effects on both the excretion of sodium and the reduction in blood pressure. There is no apparent superiority of any one of these compounds to the others. All of them may produce depletion of potassium after prolonged administration.

The mechanism of action of the hypotensive effect of the benzothiadiazine drugs is unknown. A reduction in plasma volume and cardiac output may be responsible for the initially observed moderate hypotensive effect; nevertheless the hypotensive effect persists despite re-expansion of the plasma volume.¹ Similarly the hypotensive effect persists after the prolonged administration of these drugs when plasma volume returns to pre-treatment level.

The increased reactivity of the digitalis blood vessels to pre-war substances in the hypertensive subject is decreased after the administration of the benzothiadiazine diuretics, probably because of depletion of sodium. Other investigators have implicated decreased vascular smooth muscle reactivity, altered sodium ion gradients,¹² and decreased responsiveness to infused norepinephrine.¹

The advantages of the benzothiadiazine and phthalimidine diuretics in the treatment of hypertension are these: (1) they are potent and effective orally; (2) tolerance rarely develops; (3) toxic and side effects are fairly unusual; and (4) they potentiate other antihypertensive drugs. A unique property of these drugs is their relatively unimpaired diuretic efficiency in the presence of hypochloremic alkalosis and depletion of sodium.

Toxic symptoms and side effects are

usually seen with the benzothiadiazine and phthalimidine diuretics. With each of these drugs the incidence is approximately the same. Weakness, loss of stability and mild gastrointestinal distress have been reported. Hyperuricemia with episodes of acute gouty arthritis and hyperglycemia are the most troublesome side effects. Maculopapular, petechial and purpuric skin eruptions have been described. After the administration of these drugs the blood urea nitrogen may increase. Anotemia usually occurs in patients with reduced renal function. The loss of potassium may result in a defect in total body potassium with concomitant clinical manifestations which might enhance the development of digoxin intoxication. The hypotensive response of a therapeutic dose (100 m_k daily) of hydrochlorothiazide may be equaled by the combination of hydrochlorothiazide (50 m_k) and the potassium-sparing, pyrazine diuretic, triamterene (100 m_k daily) without the edema which occurs with the administration of benzothiadiazine.¹³ Neutropenia, pancreatitis and photosensitivity are other reported side effects.

The benzothiadiazine and phthalimidine diuretics are particularly useful in combination with other antihypertensive drugs. The hypotensive effects of guanethidine, hydralazine, the Rauwolfia serpentina derivatives and the ganglionic blocking agents are enhanced by the concomitant administration of these hypotensive diuretics.¹⁴

Carbonic anhydrase inhibitors. In 1940 Mann and Keilin demonstrated that sulfonamide inhibited carbonic anhydrase. It was subsequently demonstrated by Schwartz¹ that the administration of sulfonamide to patients with congestive heart failure resulted in increased renal excretion of sodium and loss of weight. Acetazolamide was introduced for clinical use as a result of these observations. After the administration of acetazolamide there is an increase in the excretion of sodium concomitant with a decrease in the reabsorption of bicarbonate, thereby resulting in an alkaline urine associated with an extracellular acidosis. The excretion of potassium is also increased as a result of the sodium for potassium exchange which

occurs in the distal portions of the renal tubules. Increased renal excretion of potassium may persist in the absence of continued increased renal excretion of sodium with the prolonged administration of acetazolamide.

The antihypertensive activity of the carbonic anhydrase inhibitors is modest and roughly parallels their natriuretic action. There is little or no increase in the diuretic, natriuretic and antihypertensive properties of acetazolamide when the dose is increased above 500 mg daily. The renal loss of potassium that results from the administration of acetazolamide may produce clinical signs and symptoms of hypokalemia and potentiate the possibility of digitalis intoxication. Drowsiness, paresis, gastrointestinal distress, fever, leukopenia, anemia and depression of bone marrow are other reported side effects of the administration of acetazolamide. Refractoriness to the administration of acetazolamide may possibly be inhibited by the intermittent administration of the drug.

Aldosterone antagonists. The aldosterone antagonists, steroidal 17 spironolactones, are similar in structure to aldosterone. The most useful of these compounds is spironolactone which inhibits the effects of aldosterone and deoxycorticosterone thereby producing increased excretion of sodium, reduced excretion of potassium, loss of weight and hypotension in patients on a restricted intake of sodium.¹ The effects of spironolactone or aldosterone are reversed by the progressive administration of deoxycorticosterone in animals, thereby implying that these substances compete for the same renal receptor sites.

When compared to the natriuretic effect of chlorothiazide and the mercurial diuretics that of spironolactone is relatively modest. After the administration of spironolactone maximum effectiveness is achieved in approximately 3 days and after the drug is discontinued its therapeutic action may persist for a similar length of time. When administered in conjunction with either the benzothiadiazine diuretics or the mercurial diuretics it may potentiate the diuretic action of these drugs, and it is of interest to note that when it is administered in conjunc-

tion with the mercurial diuretics there may be a potentiation of the inhibition of the excretion of potassium. The hypotension associated with the administration of spironolactone is not due to the depletion of body sodium or contraction of plasma volume since the hypotensive effect is not reversed by experimental correction of these situations. The hypotensive action of spironolactone has an onset later than its natriuretic effect.^{14, 15} The magnitude of the antihypertensive action of spironolactone is comparable to that of chlorothiazide.⁷

Conflicting reports have claimed that spironolactone enhances the antihypertensive effect of the benzothiadiazine diuretics and other antihypertensive drugs.^{16, 17} It does not cause a significant decrease in blood pressure when studied in subjects controlled with placebo.⁸ It does not enhance the hypotensive effect of reserpine or guanethidine¹⁸ and does enhance the antihypertensive effect of reserpine.⁹ In order to resolve these disquieting observations we have performed a double blind study in which we compared the antihypertensive effect of spironolactone in low (25 mg daily), medium (100 mg daily) and high (200 mg daily) dosage both alone and combined with hydrochlorothiazide (100 mg daily). The statistical analysis of the results demonstrated that 100 mg daily of spironolactone had the greatest hypotensive effect.¹⁷

The side effects associated with the administration of spironolactone are fewer than those seen with the administration of the benzothiadiazine diuretics. Spironolactone, in contrast to the benzothiadiazine diuretics, does not significantly impair carbohydrate metabolism or uric acid metabolism. When administered for prolonged periods of time in large doses, weak estrogenic activity may be exhibited by spironolactone and enlargement of the breasts may result. Spironolactone may produce hyperkalemia in patients with renal insufficiency. The relative priority of side effect combined with the significant hypotensive activity is attained with the administration of spironolactone suggests that this drug has advantage over the benzothiadiazine diuretics in the treatment of hypertension.

Arloxyacetic acid diuretics. The administration of the arloxyacetic acid diuretics result primarily in natriuresis and chloruresis. There are no consistent significant deviations in the glomerular filtration rate or renal plasma flow. The sum of urinary sodium and potassium usually exceed that of urinary chloride.²² During water diuresis and in patients with diabetes insipidus after the administration of arloxyacetic acid diuretics the excretion of solute (C_s) increases, providing evidence for inhibition of proximal renal tubular sodium reabsorption and solute free water (C_{H_2O}) decreases, thereby establishing a site of action on the distal portion of the renal tubule.²³ During hydropenia the arloxyacetic acid diuretics do inhibit the production of maximally concentrated urine and do decrease the reabsorption of solute free water thereby indicating a site of action at the ascending limb of the loop of Henle.²⁴ Quantitatively the drug is more potent at the proximal site of action than at the distal sites of action.²⁵

The antihypertensive effect of the arloxyacetic acid diuretics is roughly comparable to that of the benzothiadiazine or phthalimidine diuretics.^{26,27} Unfortunately the side effects after arloxyacetic acid diuretic therapy are significant. Hypochloremic alkalosis, hypokalemia, hypervolemia with acute gouty arthritis and gastrointestinal disturbances are frequently encountered. The short duration of action of this drug necessitates frequent daily administration. The potential for blocking side effects with an antihypertensive effectiveness inferior to that of spironolactone and the benzothiadiazine and phthalimidine diuretics make it doubtful that this agent will achieve by itself a lasting place in the treatment of hypertension.

Summary

The (1) mercurial diuretics (2) benzothiadiazine and phthalimidine diuretics (3) carbonic anhydrase inhibitors (4) aldosterone antagonists and (5) unsaturated ketone derivatives of the arloxyacetic (phenoxyacetic) acid diuretics are the diuretic drugs which have been used in the treatment of hypertension. The physio-

ologic mechanisms involved in sodium chloride transport sodium for hydrogen exchange sodium for potassium exchange and water reabsorption by the kidney have been described and related to the action of the antihypertensive diuretic drug.

The two groups of drugs which are employed frequently at present are the benzothiadiazine and phthalimidine diuretics and the aldosterone antagonists. Of these groups it appears that the aldosterone antagonists (spironolactone) which have few side effects and significant antihypertensive activity have therefore some advantages over the benzothiadiazine and phthalimidine diuretics in the treatment of hypertension.

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Fundamentals of clinical cardiology

Dynamics of blood flow in stenotic vascular lesions

Simon Rodbard M.D. Ph.D.*

Durham, Calif.

A brief statement of normal arterial dynamics will serve as the basis for an analysis of the dynamics of stenotic vascular lesions.

Normal caliber

A normal artery serves as a conduit for several times the normal resting flow, with only minimal losses of pressure due to friction (Fig. 1). The volume flowing through a normal artery is determined nearly entirely by the degree of opening, i.e., conductance (rate of flow drop in pressure is the inverse of resistance) of the peripheral vessel.¹ When conductance increases, as in the hypertension of exercise, the pulsations of the vessel walls are enhanced as revealed by palpation of the arteries or by oscillometry. Since flow is laminar, vibrations are not produced and no bruit is heard.

Variations in the viscosity of the blood introduce no significant increase in losses of energy in such large vessel, although viscosity may affect flow through the arteriolar, venular, and capillary segments.

Stenosis

Narrowed vessels are the sites of drops in pressure, vibrations, and the stimulation of processes which tend to eliminate these dynamic factors.

Arteries may be narrowed by intima, by athero-plaque, or collagenlike narrowings, by

impingement of ligaments or spurs which shut on the vessel wall (Hardin)² or even by excessive force applied against the vessel by a stethoscope bell (Fig. 2). Truncal stenosis by means of compression of arteries by a sphygmomanometer cuff is utilized clinically in the measurement of the blood pressure.

Effect of peripheral vascular conductance

The extent of the disturbance produced at an arterial narrowing varies with the vascular conductance of the tissues which the vessel supplies (Table 1). When the flow of blood through the tissue is minimal, as in resting organs, a light stenosis introduces no significant impedance to the rate of flow to the tissues; the drop in pressure at the orifice is negligible and murmurs are absent.

Autoregulation. A persistent rise or fall in arterial perfusion pressure triggers intrinsic mechanisms in muscle, brain, kidney, and other tissues,³ which adjust the peripheral vascular conductance so that the rate of blood flow remains unaffected (autoregulation). Thus the fall in perfusion pressure introduced by a partial narrowing of an artery is offset with an increase in the conductance of the tissue with the result that the rate of delivery of blood remains unaffected. Such autoregulatory mechanisms can counteract the effect of slight to moderate stenosis on the rate of blood flow to certain

* From the Department of Physiology, University of California at San Diego, La Jolla, California 92037.
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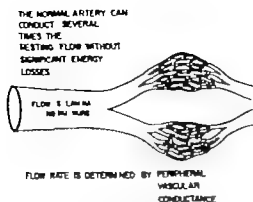


Fig. 1 Laminar flow in a large vessel. Flow through vessels of normal caliber results in minimal losses of energy. No murmurs are produced. The rate of flow in such a system is determined by the conductance of the peripheral vessel and not by the characteristics of the vessel itself.

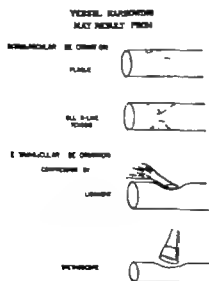


Fig. 2 Vascular narrowing may result from an intrinsic pathology of the vessel (upper drawings) or as a result of deformation from without by ligament or pressure from a stethoscope (lower two drawings).

vessels even though the pressure in the arterial segment beyond the narrowing is less than normal. An increase in activity of the tissue opens the vascular beds more widely and the pressure in the distal segment falls.

Effect of the narrowing. A narrowing impedes flow and a drop in pressure across



Fig. 3 Effect of a stenosis on the distribution of hydraulic energy (here) as a vessel (below). At the upstream segment most of the energy is evident as pressure (black) a smaller amount in the kinetic energy of velocity (dashed lines) and a small amount has already been converted to heat (hatched area) by friction especially due to vortex formation. At the orifice (shown as drawing of vessel) the velocity increases sharply at the expense of pressure and a significant portion lost as heat. Beyond the orifice the pressure rises although not to the prestenosis level and velocity approaches normal values. The amount of energy converted to heat increases progressively.

the orifice becomes evident. Flow through a stenotic orifice varies with the square root of the difference between the proximal and distal pressures¹ and with the orifice area. The rate of flow does not keep pace with the drop in pressure. Thus a doubling of the drop in pressure across an orifice increases the rate of flow by only 40 per cent ($\sqrt{200}$ per cent = 140 per cent).

When the vascular bed opens widely and the rate of flow increases greatly as after muscular exercise (Fig. 3) the stenosis becomes the limiting factor in the delivery of blood to the active tissues. The drop in pressure at the orifice and the velocity of the stream increase and vibrations are generated. However as Ljung has shown the oscillations of the poststenotic artery decrease. This effect considered by some workers to be due to arterial spasm can be accounted for entirely on the basis of the decrease in the oscillations in pressure in the poststenotic arterial segment² is associated with the increased peripheral vascular conductance of exercise.

In moderate narrowing of an arterial orifice the drop in pressure across the stenosis is of greater magnitude the duration of the resulting murmur increases

with the reduction in the drop in pressure as the thoracic pressure rises during expiration. The growth of anastomotic venous channels eliminates the drop in pressure and the bruit.

Flow through anastomoses. When arteries which supply different vascular beds are connected by anastomoses the rate of flow through each of the arteries is affected by the relative conductance of the two beds¹² and by the size of the anastomoses. When one of the vascular beds opens widely the increased rate of runoff through it lowers the pressure in its main supplying artery. The higher blood pressure in the anastomosing artery will then flow into the vascular bed which has the higher conductance and the tissue of lower conductance may receive an inadequate supply of blood. Thus in a limb with a partially stenotic arterial supply opening of the cutaneous vessels by the application of heat to the skin diverts blood from the muscles which are thereby rendered even more ischemic.

Attention has been called recently to the ischemic symptomatology which results when a narrowing at the root of the subclavian artery limits the rate of the flow of blood to the arm (Fig. 4). During rest no effects may be noted. However the marked increase in vascular conductance produced in the muscles during exercise of the arm can drain off some of the blood from the circle of Willis.

Exercise of the arm may thus precipitate an episode of cerebral ischemia in effect known as subclavian steal.¹³

Effects of this type which are more generally appreciated include the deviation of aortic blood through a ductus arteriosus and thence through the high conductance of the pulmonary vascular bed (Table II). Coarctation of the aorta beyond the ductus increases the deviation and leads to ischemia of the vessels of the lower limbs.

When the blood pressure in the two arms differs by more than a few millimeters of mercury palpation may establish a significant asynchrony of the pressure waves at the radial or brachial arteries. The indirect measurement of blood pressure in the two arms or of the delay in the transmission of the arterial pressure wave quantifies the severity of such an asyn-

At Rest

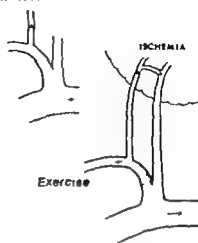


Fig. 4 Steal syndrome. At rest (upper left) flow through the aorta (see metal arrow) is distributed among the subclavian (left) and carotid arteries. The carotid (upper) vessel and cerebral arteries supply the brain through the circle of Willis. In the drawing at right a severe stenosis is shown in the subclavian artery. When exercise opens the vessels of the arm some of the blood now runs toward the head, is diverted across the circle of Willis to the vertebral artery and runs off into the limb. Conductance of the vessels of the arm. If the blood flow to the brain is compromised a symptom of cerebral ischemia will ensue.

Table II Steal syndromes

Stenosis	Ischemia
1 Subclavian + arm exercise —————	→ Cerebral
2 Femoral arterial + heating of arm — — — —	→ Leg muscle
3 Coarctation of aorta + ductus arteriosus — — — —	→ Lower extremities

tion. We have observed a number of patients with marked differences in pressure, timing and duration of the arterial Korotkoff sounds in the two arms. However the presence of such murmurs and other evidence of stenosis of the arteries to an arm is not necessarily associated with cerebral ischemia or the imminence of a cerebrovascular occlusion. The gradual modifications in vascular caliber which are induced by hydrodynamic forces may account for the benign course of this abnormality in some patients.

Hydrodynamic forces and vascular caliber

The occasional tendency for the progression of a localized stenosis^{12,17} the proliferation of collateral vessels and the development of poststenotic dilations have been attributed to the operation of hydrodynamic forces. The effects of the pressures on the walls of the vessels have excited the continuing interest of physiologists, pathologists and clinicians. In earlier studies this laboratory had discussed the possibility that it drops in pressure and increased velocities the ingrowth of the vascular lining, with a resultant progression of the stenotic tendency is facilitated. This theory has subsequently been restated in others.^{13,18} However, although the pressures in all of the arteries of the body are approximately equal the caliber of these arteries varies enormously from that of the aorta to that of the small arteries. The concept that changes in pressure affect vascular caliber is therefore without basis.

The caliber of most blood vessels varies directly with the size and activity of the vascular bed being supplied.¹⁹ This correlation as well as the tendency to progression of stenosis and poststenotic dilatation have recently been shown to result from the interaction of the stream with the wall (hydrodynamic drag).^{1,2}

As a laminar stream moves through a blood vessel the central (axial) fluid moves with relatively high velocity. Adjacent enclosing sleeves of fluid move at progressively lesser velocities. The sleeve of fluid adjacent to the wall (boundary layer) moves at minimal velocities but exerts a shearing force (hydrodynamic drag) on the endothelial cells (Fig. 5).

When peripheral vascular conductance increases the velocity of all of the laminar increases the drag of the boundary layer which acts on the endothelium also increases. It is known that an increase in the rate of flow through a vessel is associated with an immediate increase in its caliber.² This effect can be attributed to the increased drag on the endothelium which apparently stimulates a localized dilation of the smooth muscle of the vessel wall. If the increased flow is persistent the vessel will tend to be reorganized

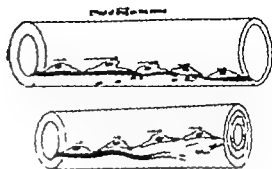


Fig. 5 The role of hydrodynamic drag in the determination of vascular caliber. In the upper drawing, the drag force in the vessel is normal drag acting on an endothelial cell. With increased drag, shear stress is applied to the endothelial cell which causes the vessel to widen acutely. This decreases the velocity of the stream and reduces drag to normal values. If the increased drag is persistent the lumen of the vessel is reorganized around a larger lumen. The free drag is indicated by the horizontal arrow. In the lower drawing a reduced rate of flow results in subnormal drag force (sketches on left). The lumen of the vessel is decreased thereby increasing the velocity and the drag force to normal values. The vessel is then reorganized around the reduced lumen.

around the larger lumen. Conversely, a reduction in peripheral vascular conductance reduces the velocity and drag of the stream and endothelial medial relationships²⁰ reduce the vascular lumen. If the reduced drag persists subendothelial proliferations and general vascular reorganization take place around a reduced lumen (Fig. 5).

A change in the drag forces on the wall thus can be considered to utilize feedback mechanisms which return the drag forces to normal values. This mechanism of normal vascular growth and atrophy can thus account for the fine adjustment of the caliber of the vessel with the blood flow through the tissues it supplies.

Depending on local circumstances the foregoing blind mechanical forces may also operate to induce progressive enlargement or progressive stenosis, either of which can threaten the integrity of the tissue or even of the individual.

Poststenotic dilatation. At a narrowing flow generates high velocities which deplete laminarity and produce vortices and turbulence in the down stream vascular segment. In a region of such nonlaminar flow

drag increases out of proportion to the volume of blood flowing through the vessel. Poststenotic dilatation can thus be attributed to the chronically increased drag beyond a region of narrowing.

Progressive narrowing. Hydrodynamic patterns can induce a progression of the stenotic process at the point of greatest narrowing in a stenosis. This effect may be attributed to the hydrodynamic conditions at the downstream end (nozzle) of a narrowing. Fluid is accelerated as it passes through the nozzle of a narrowing, gaining momentum in accord with the increase in velocity. At the downstream tip of the nozzle the high momentum of the stream lines continues to move them inward toward the central axis of the stream, thereby separating the stream from the vessel wall. The interaction of stream and wall and the hydrodynamic drag on the endothelium are minimal at such a site of separation. As mentioned above, subendothelial proliferation appears at sites of reduced drag. The tip of a stenotic nozzle is therefore a locus of increased rate of growth and thus of progressive stenosis. At some sites, as at a ductus arteriosus or a ventricular septal defect, such an ingrowth with a consequent closure of the connection may prove to be beneficial. In other sites this stenotic tendency may threaten limb and even life if

laminar flow is maintained. The announcement that the caliber of a vessel or valve is inadequate to provide for laminar flow. With further increases in peripheral vascular conductance and rate of flow, the murmur increases in intensity, pitch and duration.

Cross flow is minimal in an anastomosis between two parallel arteries which deliver blood to separate vascular beds of equal conductance. If a stenosis is present in one of the arterial roots, blood will shunt from the normal vessel to the vascular bed of the narrowed vessel. If the stenosis is severe, the deviation of blood will be marked and the tissues normally supplied by the normal vessel will become ischemic (steal syndrome).

The interaction (hydrodynamic drag) of the stream with the vessel wall determines vascular caliber. Laminar streams interact normally with the wall. The separation of the stream lines from the wall at the downstream lip of a stenotic orifice produces a locus at which stream wall interaction is minimal, with the result that the narrowing becomes progressively marked. In the poststenotic segment, turbulence increases the interaction of stream and wall and stimulates a localized enlargement (poststenotic dilatation).

Summary

A normal artery can serve as a conduit for many times the resting flow without significant loss of energy or production of murmurs. In such vessels the rate of flow is determined primarily by the peripheral vascular conductance (rate of flow/drop in pressure) rather than by the characteristics of the artery.

In a system of vessels connected in series the rate of flow is limited by the segment of lowest conductance. Thus when the conductance of the peripheral vascular bed is low, a partially stenotic lesion has no effect on the rate of flow. When an arteriovenous fistula or an increase in metabolic activity markedly increases the delivery through an arterial narrowing, the stenotic segment becomes the limiting factor and a systolic bruit indicates that the stream is no longer

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Appraisal and reappraisal of cardiac therapy

Edited by Arthur C DeGraff and Alan F Lyon

Reappraisal of digitalis Part III Electrophysiology of digitalis action

Alan F Lyon MD*
Arthur C DeGraff MD**
New York NY

The effect of the digitalis glycosides on the electrical activity of the heart is closely linked to the effect on the sodium potassium pump. The electrophysiologic effects of digitalis in the intact subject are exceedingly complex and until recent years largely unexplained. That digitalis can produce almost any arrhythmia is well known. The variety and apparent unpredictability of these reactions to digitalis can be explained by two different factors.

1. The first factor is concerned with the electrophysiologic differences between the various parts of the heart. Functional differences exist between the sinoatrial node, the specialized conducting tissue in the atrium, the ordinary atrial myocardium, the upper and lower portions of the atrioventricular node, the bundle of His, the Purkinje fibers, and the ordinary ventricular myocardium. Thus each of these parts of the heart responds to digitalis differently.

2. The second factor in the intact heart is the additional effect of digitalis that is mediated through the autonomic nervous system. It has long been known that digitalis either produces vagal stimulation or increases sensitivity to vagal discharge. The vagus mediated action of digitalis

can produce electrical effects that are sometimes similar and sometimes dissimilar to the direct effects of digitalis. It has also been suggested that some of the direct effects of digitalis are actually mediated by proadrenergic or antiadrenergic effects rather than through direct effects on membrane electrolyte movement. This adrenergic hypothesis is still controversial since the experiments that suggest it are physiologically quite complex in involving reserpination, beta adrenergic blockade, and/or surgical ablation of the sympathetic nervous system. Nonetheless, whether these studies demonstrate a key role of the sympathetic nervous system in the mediation of digitalis effect or only a permissive role, they make it clear that changes in catecholamines can profoundly modify the electrical effects of digitalis.

It is remarkable in view of all this complexity that anything has been clarified about these actions of digitalis. The tool that has been most useful in developing some understanding of these phenomena is the intracellular electrogram, which is recorded by a tiny glass electrode that can be inserted traumatically into any cardiac cell. With this electrode the intracellular electrical potentials during, and between each cardiac cycle can be recorded. When

the potential recorded are compared with those from a single electrode in the extracellular space. A record of the gradients in potential across the cell membrane can be obtained. When such a device is used to record potentials in isolated strips of the various types of cardiac tissue bathed in digitals, a precise assessment of the response of each tissue to digitals can be made. Through comparison of the results obtained in this manner with the studies of the whole heart with and without innervation and with stimulus in the intact human being, some conclusions can be drawn about the total electrophysiologic effects of digitals.

Action on undifferentiated ventricular myocardium. The intracellular electrogram when recorded from strips of tissue of undifferentiated ventricular myocardium driven at slow rates demonstrates prolongation of the last rapid phase of repolarization (comparable to the T wave of the clinical electrocardiogram). An increase in excitability, that is, a decrease in the quantity of electrical stimulation necessary to produce a propagated response, can also be shown. This stage of direct effect cannot be consistently documented in the intact heart in which it would be masked by an isolated prolongation of the relative refractory period. The first direct effect on the ventricular myocardium that can be detected in the intact heart and that occurs in the isolated strip at higher doses of digitals is a shortening of the action potential due to a reduction in the plateau or phase of slow repolarization (equivalent to the ST segment of the clinical electrocardiogram). Despite the overall shortening of the action potential, the rapid repolarization portion of the action potential is prolonged. These effects lead in the intact heart to a decrease in the absolute and in increase in the relative refractory period.

This stage of effect of digitals on the ventricular myocardium is also associated with decreased excitability. With still higher doses of digitals there is a decrease in the resting potential of the ventricular myocardium which leads directly to a decrease in the speed and size of the action potential. The clinical correlate of this is a decrease in conduction velocity.

Action on undifferentiated atrial myocardium. The data on the direct effects of digitals on the ordinary atrial myocardium are less conclusive than those on the effects on the ventricle. It would appear that at low doses there is a slowing of repolarization and prolongation of the action potential. This results in prolongation of the effective and relative refractory periods in the intact heart. These same doses slow conduction velocity and depress excitability. Higher doses in isolated strips show rapid repolarization and shortening of the action potential. Unlike the situation in the ventricular myocardium the direct effects of high doses are not easily documented in the intact heart but the effects of low doses related to a prolonged action potential are prominent in the intact heart.

Action on the Purkinje fibers. The response of the Purkinje fibers to digitals is similar to that of the ventricular myocardium with two major exceptions. (1) All of the effects occur at relatively lower doses of digitals so that for instance severe conduction disturbances may be present in the Purkinje system when conduction in the ventricular myocardium is still normal. (2) The Purkinje fibers differ from ordinary myocardium in that they have a subsidiary pacemaker function which is due to a gradual loss of resting potential during diastole. This can ultimately lead to spontaneous electrical discharge of the fiber if it is not discharged first from without. This loss of resting potential is called slow diastolic depolarization. The characteristic of spontaneous discharge is called automaticity and is common to all pacemaker tissue.

The effect of digitals on Purkinje fibers differs from that on ordinary myocardium in that the drug also affects slow diastolic depolarization. It leads to an increase in the rate of such depolarization and to an increase in automaticity. This may ultimately lead to discharge prior to the sinus pacemaker and to ventricular premature contractions and ventricular tachycardia. Usually the shortening of the refractory period that occurs in the Purkinje system is quite uneven so that recovery time varies from fiber to fiber. These variations in recovery and conduction in the Purkinje

system can lead to differences in the sequence of repolarization in different parts of the heart. This is the cause of the digitalis-induced S-T changes of the clinical electrocardiogram.

Action on the sinoatrial node Like the Purkinje fibers the sinoatrial node is specialized pacemaker tissue that manifests slow diastolic depolarization. It differs from the Purkinje fibers in that it is less rather than more sensitive than the surrounding myocardium to the direct effects of digitalis and in that the direct effect that does occur is a decrease rather than an increase in automaticity due to prolongation of slow diastolic depolarization.

Action on the atrioventricular node Perhaps the most important electrical action of digitalis is to decrease conduction through the atrioventricular node. Digitalis produces a measurable increase in the effective refractory period of atrioventricular nodal tissue in the intact heart. This is apparently not due to an increase in the duration of the action potential but to a failure of propagation of the impulse. In this situation the portion of the atrioventricular node stimulated may actually depolarize but conduction is so poor that the impulse is not transmitted to nearby cells from which it can be recorded. Thus this prolongation of the effective refractory period is actually a conduction effect.

Vagal action of digitalis The vagal action of digitalis that is those effects on the electrical activity of the heart that are produced by either increased vagal stimulation or increased responsiveness to vagal stimulation is limited to the area of vagal innervation: the sinoatrial node, the atria and the atrioventricular node. The important vagal effect on the sinoatrial node is the same as the direct effect: a decrease in automaticity due to a slowing of slow diastolic depolarization. The vagal effect on the ordinary atrial myocardium on the other hand is opposite to the major direct effect in that it tends to shorten, of the absolute and relative refractory periods. Only the upper and mid portions of the atrioventricular node are sensitive to vagal stimulation. In these regions the effect is similar to that produced directly

by digitalis leading to a further interference with conduction.

Net effects on the innervated heart in the areas innervated by the vagus The net effect of moderate doses of digitalis on the innervated heart reflects primarily the vagal actions of the drug. There is a decrease in sinoatrial automaticity, a decrease in atrial excitability, a shortening of the effective refractory period, a slowing of conduction in the atria and a depression of the transmission of impulses in the atrioventricular node. Below the atrioventricular node the direct effects are predominant. Thus there is an increase in the automaticity and a decrease in the conductivity of the Purkinje fibers and a decrease in the conductivity, excitability and refractoriness of ventricular myocardium.

Electrophysiologic effects on the human heart Except in the presence of atrial fibrillation in which case the decrease in conductivity in the atrioventricular node is helpful in controlling the ventricular rate the electrophysiologic effects of digitalis have little clinical influence in the therapeutic range and become important only when toxic doses of the drug produce arrhythmias. What can be seen with therapeutic doses are sagging S-T shifts reflecting a shift of the vector of slow repolarization away from the QRS. These changes may or may not involve the T wave which sometimes shows peaking and sometimes shows inversion. In any case these repolarization changes have poor correlation with either therapeutic or toxic effect.

The slowing of the sinus rate frequently produced by digitalis in lower animals is not seen in normal man in whom no change in the resting or exercise rate can be documented. The only evidence of increased vagal activity that can be found in normal man is an increase in the frequency of sinus arrhythmia. The decrease in pulse rate that occurs with digitalization in patients with congestive heart failure probably reflects an increase in stroke volume rather than a direct electrophysiologic effect. The increase in pulse rate on standing, recorded after injection of histamine, probably reflects a decrease in venous return. An increase in the T-R

interval does not occur consistently. The increased automaticity of Purkinje fibers that occurs at slow rates is not important so long as the rate of supraventricular discharge is faster and there is no heart block.

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Annotations

Differential actions of polypeptides and other drugs on coronary inflow vessels

Considerable controversy exists as to whether vasopressin and its synthetic analogues can constrict arterial and venous smooth muscle to contract. Such knowledge of the differential vascular effects of these neurohypophyseal polypeptides is necessary for at least two reasons: (a) the suggestion that these hormones may play a role in the local regulation of blood flow in modulation of vascular smooth muscle responses to other vasoconstrictor substances and (b) their possible therapeutic value in the treatment of shock. Although these neurohypophyseal polypeptides exhibit elective and paradoxical effects in the microcirculation¹ which are beneficial in experimental shock,² some of these analogues have been reported to induce marked coronary arterial constriction and arrhythmias in dogs, guinea pigs and rabbits.³ Such detrimental effects if found in the human myocardium would obviate the use of these drugs class A, PLV 2 (2-phenylisalanine 8), or vasopressin; on the other hand has been reported (a) to increase the relative myocardial blood flow in rats and (b) to be a tachyarrhythmic in the cat (free from inducing arrhythmias in man).⁴

In view of the foregoing, species differences, it was thought to be worthwhile to examine the influence of sanguine anoxemia and PLV² on isolated coronary arteries divorced from the *in vivo* effects of an overall metabolism. However, because of possible segmental differences in coronary arterial reactivity, we thought that it was not feasible to examine all three major coronary arteries (left coronary, left coronary, and circumflex ar-

Freshly removed bovine beef hearts (within 10 to 15 min after slaughter) were washed and placed in normal mammalian air hunger solution (8.6 mM NaCl, 0.3 mM KCl, and 0.33 mM CaCl₂ per liter). After being drenched from the myocardial helical strips (4 by 25 mm) of all the experimental types were prepared and suspended isometrically under 1 gram of tension and incubated in 30-ml non-de-aerated control gas bubbles per beat per minute (composition 10 mM H₂O, 1 mM per liter NaCl).

12.0 KCl 4.7 NaH₂PO₄ 1.18 MgSO₄ 7H₂O
1.18 NaHCO₃ 2.0 glucose 0.33 CaCl₂ 2.52 EDTA
0.076) at 37°C through which 95 per cent O₂
and 5 per cent CO₂ was bubbled. Force of contrac-
tion was measured with a Sanborn FTA 10-1 trans-
ducer and recorded on a heat writing oscillograph
(Sanborn Model 150). Two hours after the prepa-
ration were incubated under tension, the effects
of various drugs were examined. A total of 70 prepa-
ration dissected from 5 hearts was utilized for
the present report.

isoprenes in 8 angiotensin isoprenes in up to 10 L per milliliter) or ELA 2 (up to 0.5 L per milliliter) failed to induce contractions in any of the different coronary trunks. However, both isoprenes and PLA₂ (Fig. 1) produced relaxation in all three types of vessels after all arguments were induced to contract with a variety of tetraoctadecylphosphor substances e.g. histamine, serotonin, KCl, acetylcholine and angiotensin. In BaCl₂-induced contractions, however, could not be relaxed by isoprenes or PLA₂. It should be mentioned that relaxation induced by PLA₂ were greater than those induced by isoprenes in all respects both to magnitude and rate.

Although contractions were induced in all three segments with $4 \text{ } \mu\text{M}$ BaCl_2 or $1 \text{ } \mu\text{M}$ tannic acid, the three segments of esal exhibited wide differences in sensitivity (Fig. 7). Atracurium (up to $30 \text{ } \mu\text{g}$ per ml liter) and angiotensin (up to $50 \text{ } \mu\text{g}$ per ml liter) induced contractions only in caudal segment whereas veratrum had no contractile effect on least in outer third (Fig. 7).

Norepinephrine, epinephrine and the sons of peptide had a α_1 caused an increase in all three types of vessels (Fig. 1, 2). It should be noted that both the degree and rate of relaxation on II cases was limited by the amount of tenon initially induced by the smooth contractile agents. The greater the initial development on the less the rate and maximum time of the relaxation on Norepinephrine.

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Rheumatic fever without clinical evidence of carditis The necessity and efficacy of chemoprophylaxis

Rheumatic fever without clinical evidence of carditis today account for over one half of the total episodes of acute rheumatic fever and in the adult acute rheumatic fever is even more frequently characterized by the absence of carditis. The purpose of this study was to determine that patients who had rheumatic fever without clinical evidence of carditis particularly in regard to the probability of consequences of rheumatic carditis and the necessity of efficacy of chemoprophylaxis.

Our study group consisted of 33 patients with adult acute rheumatic fever without clinical evidence of carditis who were being followed at the Cardiology Department of the University of

Georgia Heart Association Cardiac Clinic throughout the study. The control group was composed of 312 patients who had clinical evidence of carditis. The diagnosis of acute rheumatic fever was made in accordance with the modified Jones criteria and carditis was diagnosed by the definition of the American Heart Association Chemoprophylaxis when given was administered recommended by the American Heart Association.

The group of patients without clinical evidence of carditis consisted of 136 males, 54 Negroes and 82 whites and 196 females, 119 Negroes and 77 whites. The average age of the patients at the time of the initial attack of acute rheumatic fever was 10.1 years and at the time of the study was 17 years.

At the University of Georgia, the patients with

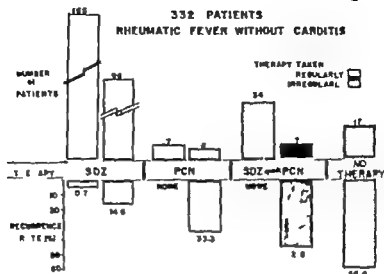


Fig. 1. See text.

rheumatic fever without clinical evidence of carditis had recurrent rheumatic fever with a total of 103 per cent recurrent episodes. The average age at the time of the rheumatic fever was 13.3 years with a range from 1 to 18 years. In the initial episode of recurrent rheumatic fever, 44 per cent of patients had the initial episode of acute rheumatic fever after 21 years of age and none of these patients had a rheumatic recurrence.

Both the initial and recurrent episode of acute rheumatic fever were predominantly distributed throughout the months of the year.

Of the 332 patients who had rheumatic fever without carditis (111 chemoprophylaxis with sulfadiazine had been prescribed for 261 and with penicillin for 13 and 41 patients had been changed from sulfadiazine to penicillin or vice versa with a change of drug sensitivity. Chemoprophylaxis had not been prescribed for 17 patients.

Of the 261 patients in the sulfadiazine group 165 took the drug regularly and 96 irregularly. Seven patients in the penicillin group took the antibiotic regularly and 6 irregularly. In the mixed sulfadiazine penicillin group in whom the indication had been changed because of drug sensitivity 34 patients received the chemoprophylaxis regularly and 7 irregularly.

Only 1 patient had a recurrence of rheumatic fever while on regular chemoprophylaxis. There was a 0.7 per cent recurrence rate representing the one patient in the group taking sulfadiazine regularly, a 14.6 per cent recurrence rate in the group taking sulfadiazine irregularly, no recurrences among patients regularly on penicillin or mixed sulfadiazine penicillin prophylaxis and a 33.3 and 47.8 per cent recurrence rate respectively among the groups on penicillin irregularly and mixed sulfadiazine penicillin prophylaxis irregularly. Note that over one half of the patients 58.8 per cent who were

not prescribed chemoprophylaxis had recurrent rheumatic fever.

These data represent a total of 2415 patient years of follow-up of patients with rheumatic fever without clinical evidence of carditis—1349 patient years of regular chemoprophylaxis and 1176 patient years of irregular or no chemoprophylaxis.

These 332 patients who had acute rheumatic fever without clinical evidence of carditis were further characterized with regard to chemoprophylaxis (Table 1). The 206 patients who were regularly receiving chemoprophylaxis were separated from the 126 patients who were receiving irregular or no chemoprophylaxis. The average age of the patients at the time of onset of rheumatic fever was 9.93 years in the group on regular chemoprophylaxis.

Table 1. Three hundred and thirty-two patients with rheumatic fever without carditis

	Regular chemoprophylaxis	Irregular or no chemoprophylaxis
Number of patients	206	126
Average age at time of initial episode of rheumatic fever (yr.)	9.93	10.03
Average duration of follow-up (yr.)	6.55	8.9
Recurrence (per cent)	0.49	3.0

almost identical with the 10.03 years in the group on irregular or no chemoprophylaxis. The patients receiving prophylaxis were followed for an average of 6.55 years, a significantly greater average follow-up 8.9 years as recorded for the group on irregular or no chemoprophylaxis. Indeed some patients in the latter group antedated the era of chemoprophylaxis for rheumatic fever.

Only one patient in the group on regular chemoprophylaxis had recurrent rheumatic fever for a recurrence rate of 0.49 per cent. In the group receiving chemoprophylaxis irregularly or not at all 39 patients had recurrent rheumatic fever for a recurrence rate of 23 per cent. We believe that this markedly greater recurrence rate is due to the omission of chemoprophylaxis and cannot be explained merely by the longer duration of follow-up.

In our group of 332 patients who had initial attack of acute rheumatic fever was not associated with clinical evidence of carditis, the rheumatic recurrences tended to be of a mimetic nature, i.e., patients who did not have carditis with the initial rheumatic episode did not have carditis with the recurrent episode. We have followed only one patient whose recurrence was not mimetic; he had rheumatic polyarthritides without carditis at age 6 and at age 74 he had recurrent rheumatic fever characterized by arthritis, by pericarditis (manifested by friction rub) and by myocarditis (manifested by A-V dissociation on the electrocardiogram). At present it has been 3 years since the recurrent episode and he has shown no residual valvular damage.

The sex, race, and age distribution of the control group of 317 patients with rheumatic fever without carditis was comparable to that of the group with clinical evidence of carditis. However, the group with carditis had a significantly smaller recurrence rate of rheumatic fever than that of the group without

carditis—4.7 as compared to 9.1 per cent. These data appear to contradict the reports in the literature which show an increased recurrence rate of rheumatic episodes among patients with carditis. However, in our group without carditis, significantly more patients either were not prescribed chemoprophylaxis or more commonly were not taking chemoprophylaxis regularly, 33 per cent in the group without carditis as compared to 22 per cent in the group with carditis. The study group without clinical evidence of carditis thus had a significantly greater number of patients receiving chemoprophylaxis irregularly or not at all and a concomitantly significantly greater number of patients with recurrent rheumatic fever than did the control group with carditis.

In summary, a group of 332 patients whose initial episode of acute rheumatic fever was not associated with clinical evidence of carditis, there was a recurrence rate of rheumatic fever of 9.1 per cent. Recurrent episodes occurred throughout the year and for a considerable number of years after the initial acute episode. Rheumatic recurrences were encountered almost exclusively among patients receiving inadequate or no chemoprophylaxis. Patients without clinical carditis during the initial attack of acute rheumatic fever usually escaped apparent cardiac damage during recurrent episodes; the recurrences tended to be mimetic. Long-term year-round chemoprophylaxis recommended to prevent the recurrence of rheumatic episodes in patients with rheumatic fever without clinical carditis despite the apparent benign nature of the recurrence.

Vandie Kass Wenger, M.D.

Robert Leonard, M.D.

Ben Bern, M.D.

Emory University School of Medicine

69 B He. B. S.E.

Atlanta 3, Ga.

Primitive bulbus cordis and idiopathic hypertrophic subaortic stenosis in man

The current emphasis of studies on the physiologic mechanism and etiological understanding of idiopathic hypertrophic subaortic stenosis has revived interest in the comparative anatomy and physiology of the bulbus cordis.

The bulbus cordis is an important structure with important bearing on function in heart. The bulbus cordis contains distinct anatomic structures and remains functionally significant through the reptile species. Cineangiogram on tortoise has demonstrated the following features:

contraction of the bulbus cordis and the persistence of contraction during diastole. These features are observed in patients with idiopathic hypertrophic subaortic stenosis. It has been noted that the contraction of the bulbus cordis is nonmammalian type as exaggerated under the influence of adrenaline during adrenergic action. In tortoise, the functional behavior of the right ventricle outlet tract has been demonstrated. More recent reports have stated the use of which left ventricular pressure gradients can be produced in

HANDBOOK OF CARDIOLOGY FOR NURSES By Walter Modell M.D. F.A.C.P. Doris R. Schwartz M.A. R.N. Leon S. Hartzline M.A. R.N. and Frederic T. Kurland Jr. M.D. New York 1966 Springer Publishing Company Inc. 323 pages Price \$4.75

This fifth edition on cardiology for nurses outlines in a few pages some of the common problems and definitions in cardiology. The fact that the handbook has reached the fifth edition attests to its success and excellent reception and is evidence that an educational need is being met. However from the reviewer's point of view the book lacks advice on how to nurse the patient with heart disease and how to handle the special problems. The book is primarily a course in clinical cardiology which is presented very well in a few pages. The book does assist the nurse in understanding cardiology better. It is up to date and is supported by a few illustrations and a good index. It is hoped that the sixth edition will include extensive practical instructions and advice necessary to good nursing of the patient with heart disease. This book on cardiology is recommended to nurses as a valuable source of instruction on aspects of heart disease and its treatment.

SECOND SYMPOSIUM ON CATECHOLAMINES Edited by George H. Ackerson M.D. reprinted from *Pharmacological Reviews* Vol 18 No 1 March 1966 Published for the American Society for Pharmacology and Experimental Therapeutics by Williams & Wilkins Company Baltimore 1966 803 pages Price \$15

This is an authoritative summary of the pharmacology and physiology of the catecholamines. The symposium was held at the Istituto di Ricerche Farmacologiche Mario Negri Milan Italy July 4-9 1965. Everyone who is interested in catecholamines will find this to be an excellent book. It is highly recommended as a very comprehensive and reliable source of information on an important subject.

CONFERENCE ON PULMONARY CIRCULATION Oslo 1965 Edited by Carsten Væller Oslo 1965 (in Norwegian) 212 pages

This is a summary of the symposium on the pulmonary circulation held in Oslo during September 1965. The conference was concerned with six main topics namely pulmonary motor regulation physiology and pathophysiology of the pulmonary capillary pulmonary blood flow pulmonary vascular resistance pulmonary vascular regulation in heart disease and pulmonary hypertension. The participants were from Denmark Finland Norway and Sweden. These papers therefore reflect Scandinavian work and are on a very important subject. There are two separate reports which are on the third and interesting. Each paper is followed by a summary of the discussion on all the aspects of the conference. This is a good book.

L. HYPERTENSION ARTERIELLE (Arterial Hypertension) Edited by Paul Milliez and Philippe Tcherdakoff Paris 1966 L'Expansion Scientifique Française 524 pages

This represents the proceedings of the first meeting of the International Club on Arterial Hypertension held July 27 1965 in Paris. The proceedings include several papers on (1) hypertensive factors of the kidneys (2) hypertensive factors of the kidneys (3) aldosterone (4) hypertension with renal artery lesions and (5) hemodynamics. The conference as reflected in this book apparently was conducted much like the well known and extremely successful Cuba Symposium. Many papers are included in this book with a bibliography and the discussions which followed the presentation of each paper. The text are in English and French more in the former language. Those who follow the field closely may not of course wish to read the book to learn what has been said but will find little new whereas others who wish to learn the present concepts will find the book to be useful and a source of ideas for investigation. The book is nicely printed and bound in leather.

SYMPOSIUM IN MEDICAL RESEARCH Volume II By Robert F. Rushmer Editor in Chief Chicago 1966 Year Book Medical Publishers Inc. 301 pages Price \$10.50

This is a good handbook. The tradition of presenting brief discussions of current methods and related problems in medical research is maintained. Several brief well-presented and well-illustrated papers are concerned with the main topics in the pocket handbook. The topics discussed are (1) measurement of diaphragm tension and pressure (2) quantitative method for measuring the microcirculation and (3) neurophysiological techniques. The contributors are experts in their respective fields and the problems discussed are among the most difficult in physiology. This is a good handbook and highly recommended to physiology and medical students.

Book received

DIETARY FAT AND HEALTH A Report of the National Nutrition Board National Academy of Sciences National Research Council Publication 114 National Academy Press Washington 531 pages Price \$1.50

Announcement

THE FORTIF ANNUAL CONFERENCE SEMINAR SELECTED TOPICS IN CARDIOLOGY (cardiophysics, diagnosis and use of electrocardiograph and therapy) presented by The Fortif Heart Fund will be held at the Fortif Club Resort on Beach 31, December 1 through 4, 1966.

Attendance is free. It will include Edward Demery, M.D., Atlanta, Georgia; Vernon M. C. F. in

London, England; Joseph Serfati, M.D., Washington, D.C.; Demetrius Schellert, M.D., Mexico City; and Cuthbert Withers, M.D., August, Georgia. The seminar will be hosted by Henry Murphree, M.D., Metairie, Louisiana.

For further details write Dr. Rogers Hunt, Fortif Fund, Box 500, Fort Lauderdale, Florida 33304.

Acknowledgment to reviewers

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Editorial

The prevention of coronary heart disease

Alexander R. P. Walker D.Sc.
Johannesburg, South Africa

In a recent investigation undertaken in London¹ the survival rates of two groups of patients with coronary disease were compared: one on a reduced intake of fat and the other on their usual self chosen diet. Since no advantage accrued to the experimental group the conclusion was reached that a low fat diet has no place in the treatment of myocardial infarction. Others have voiced similar views. It seems to be somewhat premature that an ineffective change in one factor of a disease known to have protein aetiology should lead to the outright rejection of that single factor in the treatment of the disease. Within the last generation there has been a legion of contributions seeking to elucidate apportion blame and make recommendations in relation to the different factors which promote or cause coronary heart disease (CHD). As is well known factors accepted as being of prime importance at least among Western populations are diet, activity, stress, smoking, hypertension and overweight. Currently there are three main hypotheses each recording dominant influence to a single factor: namely (1) diet,² (2) activity,³ and (3) stress.^{4,5} In respect to diet there is a difference of opinion concerning the influence of individual components, namely

(a) fat⁶ and (b) sugar¹¹ and in relation to fat there is a division regarding the role of (i) saturated and unsaturated fats^{7,8} and (ii) essential fatty acids.^{9,10}

Although some doubt the extent of the increase that has occurred in mortality from CHD¹² none is under any illusion as to the magnitude of the public health problem involved. Among sophisticated populations the two highly practical questions at issue are these: (1) Does a significant decrease in premature deaths ensue if the offending factor or factors (whether in excess or short fall) are modified or corrected? (2) Does it lie within the power of such population to make the changes called for?

In the first place it is well to face the somewhat ironic situation in which certain of the factors enumerated above may be observed to be operating singly or in combination among primitive technically retarded or unsophisticated populations and yet their presence is consistent with the virtual absence of the disease. Such freedom is seen in the Navajo Indians in the Central African Massai, Samburu¹³ and Rendille¹⁴ despite a high intake of fat and in the Mountain Apache in rural Japan¹⁵ and in Moroccan Jews in spite of considerable hypertension. Such

freedom is also seen in the South African Bantu in urban areas there is a by no means insignificant minority of individuals who outwardly at least have many of the same characteristics which are known to conduce to CHD in whites yet the disease remains rare.^{1,2} Evidently different populations in different contexts may react differently to a given stimulus or as Lowenstein³ has it "a factor or factors deleterious in one human context may be largely or wholly innocuous in another. This phenomenon is neither unique nor novel; it has counterparts in other spheres of human experience. For example in Durban South Africa there is very roughly the same prevalence (about 10 per cent) of *Endomorpha histolytica* in the stools of Africans, Indians and whites in Indians and whites the organism lives innocuously and is largely non-symptomatic but in Africans the organism is often present in a fulminating invasive form causing severe illness and sometimes death. What is it that in one population but not in another catalyzes or energizes a potentially noxious component to become malignant?"

This leads to another question. Does epidemiological information on populations in which CHD is very uncommon have any serious bearing on the changes required to alleviate progress to CHD in sophisticated populations? Often it is regretted that if only we could adopt a feature or features of this or that primitive or other population CHD would no longer be the enormous problem that it is today. But a white person does not become a Bantu just by lowering his intake of fat or his level of cholesterol nor a Maori simply by considerably increasing his habitual activity nor upon request or with intention does he become relaxed and lose his CHD prone personality merely by resolving that it shall be so. I believe that the CHD prone segment of a population should aim at attaining the relevant characteristics of the CHD less prone segment of that same population rather than seeking to emulate this or that feature of other populations of the type mentioned.

Bearing in mind the hypothesis propounded let us turn now to the main questions at issue. In a given CHD prone segment of population how far can persons

perhaps late in life even with the utmost willingness project themselves into another context? There are groups with low prevalences of CHD such as the elderly but very active Swiss mountain farm workers.⁴ Can the relevant protecting features including presumably their regular and tranquil manner of life really be adopted? In a recent study in Norway⁵ it was shown that certain farming communities as compared with the population of Oslo have a threefold lower mortality rate from arteriosclerotic and degenerative heart disease and also from cancer. Can the sophisticated man of Oslo hope to take on the necessary protective features of the rural farm worker's life? Or can the elderly in Bucharest⁶ incline toward the life led by the Danube delta fishermen? Then there are the Seventh Day Adventists.^{7,8} Does adoption only of their diet non-smoking habits etc. confer the lower prevalence of CHD that they enjoy? What of the role of their religion and philosophy? Crucially in the segments of population mentioned is having lower CHD just what features have to be taken on?

In recognition of our uncertainty over the answers to these questions not to speak of the difficulties of conformation involved the view held by many is somewhat indeed heavy⁹ has stated that although

there is still no final proof that the reduction of serum cholesterol level will substantially alter the risk of subsequently developing CHD it is suggested as a possible prophylactic measure. In one evaluation of the Birmingham study¹⁰ it is admitted that despite an explosive expansion of research in lipid metabolism very little is known of the principal determinant of regulation of serum cholesterol level. Morris¹¹ concurs believing that the etiology of high blood cholesterol remains an urgent problem on which both genetic and environmental data at present are grossly deficient. Russell¹² goes further and considers that it seems unlikely that management directed solely at reduction of blood cholesterol without simultaneous efforts to neutralize psychophysiological mechanisms induced by environmental stress can be significantly effective. The regret expressed in a recent

review was that it will prove difficult to modify certain trends in sophisticated affluent communities.²⁴ In a World Health Organization Study Group Report²⁵ it was concluded that there is no effective means of reducing CHD. Another writer has noted that we are as helpless against the ravages of cardiovascular degeneration as were our ancestors against plague.²⁶

But are the views which would seem to be the nadir of despondency warranted? In certain countries in war time involuntarily imposed changes in diet, activity and pattern of life were associated with a strikingly abrupt fall in the death rate from ischaemic heart disease.²⁷ The most apposite analogous but peace time situation known to the writer concerns white South African long term prisoners who conform in measure to the dietary pattern and manner of life of the Bantu. During confinement such prisoners have a negligible number of episodes of CHD or deaths due to it.²⁸ In the period 1960-1965 in the main prisons for long term of offenders among 2450 persons who were 20 years old and upward there was an annual average of 3 episodes of and 1 death from CHD. In an age matched male population in Johannesburg deaths were about 8 times more common. The low prevalence of CHD in the prisoners is in agreement with similar reports on inmates of federal penitentiaries.²⁹

The burden of foreboding borne by the patient with coronary disease has been commented on in a recent editorial.³ Despite the foregoing it is not believed that the outlook is hopeless. It is certainly not entertained that current investigations such as those of the Anti Coronary Club and the National Diet Heart Study³⁰ are not eminently worth while they may well yield extremely valuable results. In the meanwhile the balanced recommendations both for the patient with coronary disease³¹ and for the anxious or coronary disease prone person have been ably set out. Russell³² has provided evidence which suggests that those who stop smoking considerably lower their proneness to CHD. Stamler³³ in no means rules out a breakthrough in research and has recently stated that the ability to control the major risk factors by safe medical

means holds out the very real possibility of achieving primary prevention of premature clinical atherosclerotic disease whether coronary, cerebral or peripheral.³⁴

Nevertheless I am driven to consider that in spite of the knowledge available the bulk of the patients with coronary disease and certainly the bulk of the coronary disease prone moiety of the population either elect not to or cannot reorientate themselves to the magnitude of the changes required of them for significant relief from susceptibility. It is considered that the large scale altering of the requisite factors for reducing proneness to CHD is scarcely possible in a free society that this can only be achieved in situations in which a measure of coercion prevails.³⁵ as indicated in the two examples given.

Achilles and Odysseus in Hades. Rather would I be a slave in a proper home and be above ground than be a king of kings among the dead. But in the times of Homer there were perils from famine and war and pestilence and life was brief. Nowadays when far more people live much longer it would seem to be incapable that most people prefer to continue to pursue their habitual way of life which at least has not the physical rigor of the past and to accept the risks of degenerative disease which are implicit in the manner of life prevailing risks which may well be increased by every milestone of socio-cultural economic advancement—the rapid growth of the middle class the affluent society the New Frontier the Great Society.

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Clinical communications

Hemodynamic sequelae of atrial, ventricular, and sequential atrioventricular pacing in cardiac patients

Philip Samet MD*

Cesar Castillo MD

William H Bernstein MD

Miami Beach Fla

Earlier studies from this laboratory have emphasized the role of atrial systole in the maintenance of ventricular function.¹⁻³ Comparable data have been obtained by others both in the experimental animal and man.⁴⁻¹⁰ The aforementioned studies have demonstrated that atrial pacing results in larger cardiac outputs than does ventricular pacing at the same rate in subjects in sinus rhythm.¹⁻³ Since these differential effects of atrial and ventricular pacing may be due either to the role of atrial systole or to the role of aberrant ventricular depolarization further studies were planned to differentiate between these two possibilities. The development of a paired pulse pacing unit (Medtronic) permitted utilization of a third type of pacing: sequential atrioventricular pacing. In this form of pacing, one stimulus is applied to a bipolar catheter in the right atrium and a second stimulus is applied to a similar catheter in the right ventricular outflow tract at a prefixed interval somewhat less than the normal P-R interval for that particular patient. In this fashion the normal relationship between atrial and

ventricular mechanical activity is maintained but an aberrant pathway of ventricular depolarization must of necessity be utilized. Sequential atrioventricular pacing thus permits a decision as to whether the different effects of atrial and ventricular pacing are due to aberrant pathways of ventricular depolarization or to absence of synchronized atrioventricular activity in ventricular pacing.

Materials and methods

Thirty three patients with pulmonary emphysema with or without cor pulmonale and 27 subjects with rheumatic heart disease were studied. Eighty nine comparisons of cardiac output during atrial, ventricular and sequential atrioventricular pacing were made in the group with pulmonary emphysema: 7 at rates 60-89 beats per minute, 33 at rates 90-109, and 49 at rates 110-140. Eighty similar comparisons were made in the group with rheumatic heart disease: 19 at rates 60-89 beats per minute, 39 at rates 90-109, and 26 at rates 110-140. The three varieties of pacing employed were described above.

Two 31-125 cm long, bipolar electrode catheters were passed one into the right atrium and a second into the right ventricle. A third catheter was passed into either the pulmonary artery or the left atrium by the transseptal left atrial puncture technique to serve as a vehicle for injection of 2.5 to 3 mg. of indocyanine green for indicator dilution determination of cardiac output. The dye curves were inscribed by a paration of blood from a systemic artery with an indwelling Courind needle via a Harvard constant infusion withdrawal unit and Gilford densitometers. The dye curves were recorded on an 8-channel Electronics for Medicine recorder and were calibrated by three dye in blood concentration levels. The semilog replot extrapolation method was used to calculate cardiac output. Measurements of flow were made at 1 to 2 minutes after the institution of any given rhythm.

Results

The group with pulmonary emphysema will be discussed first. The mean indices for the entire set of 69 studies were 2.60, 2.06 and 2.31 min/M for atrial, ventricular and sequential atrioventricular pacing, respectively. The difference between atrial and ventricular pacing was significant ($p < 0.001$); the same was true for the difference between ventricular and sequential atrioventricular pacing. The difference between atrial and sequential pacing was only significant at the 0.05 level ($p = 0.05$). The essential data are plotted in Figs. 1-3.

For the 60-89 rate group, the mean indices for the set of 7 for atrial, ventricular and sequential pacing were 2.46, 2.16 and 2.48 $\text{L}/\text{min}/\text{M}$, respectively. The ventricular pacing index differed from the other two ($p = 0.05$). There was no difference between atrial and sequential atrioventricular pacing. For the 90-109 set of 33 observations, the mean indices for atrial, ventricular and sequential pacing were 2.58, 2.00 and 2.48 $\text{L}/\text{min}/\text{M}$, respectively. The ventricular mean index differed from the other two ($p < 0.001$). Atrial and sequential pacing levels were also significantly different but only at the $p = 0.05$ level. For the 110-140 set of 49 observations, the mean indices for atrial

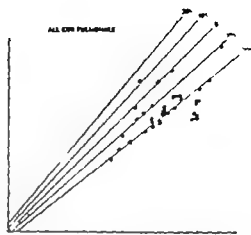


Fig. 1 Comparison of cardiac indices during atrial and ventricular pacing at all three groups of heart rates tested. The zero line is the line of identity. Ten and 20 per cent are deviations from the line of identity. The patient group is that of pulmonary emphysema and/or cor pulmonale.

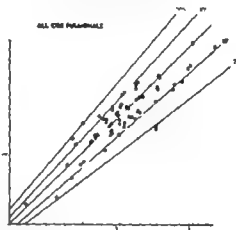


Fig. 2 Comparison of cardiac indices during atrial and sequential atrioventricular pacing.

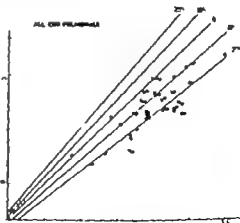


Fig. 3 Comparison of ventricular and sequential atrioventricular pacing in patients with pulmonary emphysema and/or cor pulmonale.

ventricular and sequential pacing were 2.63, 2.09 and 2.57 L/min/ M^2 respectively. Ventricular pacing levels were significantly different from the other two pacing levels $p < 0.001$. There was no difference between atrial and sequential pacing.

The 80 observations in the group with rheumatic heart disease will be discussed next. The mean indices for the entire set were 2.79, 2.29 and 2.70 L/min/ M^2 for atrial, ventricular and sequential pacing respectively. The ventricular pacing index was significantly different from the other two levels $p < 0.001$. The differences between atrial and sequential pacing were different only at the 0.05 level $p = 0.05$. These data are shown in Figs. 4-6.

For the 60-89 rate group, the mean indices for the set of 15 observations were 2.85, 2.47 and 2.74 L/min/ M^2 for atrial, ventricular and sequential pacing respectively. The atrial and ventricular means differed $p < 0.001$. The ventricular and sequential means differed $p = 0.05$. The atrial and sequential means were not significantly different. For the 90-109 rate group, the mean indices for the set of 39 observations were 2.84, 2.32 and 2.71 L/min/ M^2 for atrial, ventricular and sequential pacing respectively. The ventricular level differed from the other two means $p < 0.001$. The atrial and sequential means also differed $p = 0.001$. For the 110-140 rate set of 26 observations, the mean indices were 2.68, 2.18 and 2.65 L/min/ M^2 respectively for atrial, ventricular and sequential pacing. The ventricular levels were significantly different from the other two levels $p < 0.001$. The atrial and sequential means were not significantly different.

The electrocardiogram during sinus rhythm, atrial, ventricular and sequential atrioventricular pacing is shown in Fig. 7. In 5 patients in these two groups (rheumatic heart disease and pulmonary emphysema), multiple measurements of cardiac index were made at repeated intervals after the institution of sequential atrioventricular pacing. At 0-2 minutes, 2-5 minutes and 5-7 minutes, the average indices were 2.62, 2.44 and 2.69 L/min/ M^2 respectively, demonstrating that valid measurements of flow may be made within 1 to 2 minutes

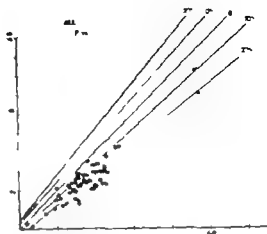


Fig. 4 Comparison of atrial and ventricular pacing at all three groups of heart rates studied in patients with rheumatic heart disease.

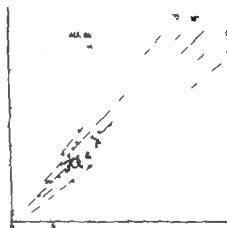


Fig. 5 Comparison of cardiac index during atrial and sequential pacing.

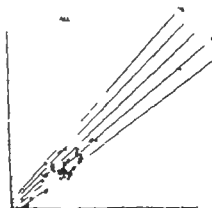


Fig. 6 Comparison of cardiac index during ventricular and sequential pacing at all three groups of heart rates.

PUL EMPHYSEMA PACING TECHNIQUES

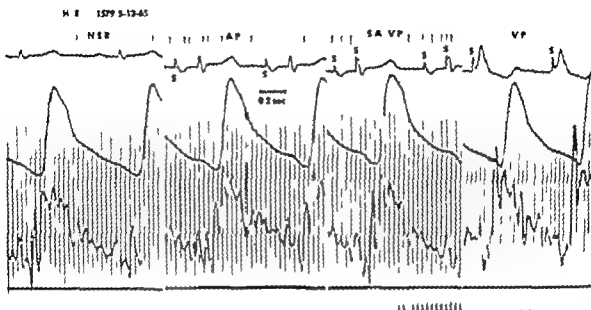


Fig 7 Various type of pacing technique employed in this study. S refers to the stimulus applied to the atrial or ventricular bipolar electrode catheter or to both catheters.

after the institution of a given pacing rate.

Further statistical analyses are of interest. For all ranges of heart rate there was no difference for the difference between atrial and ventricular pacing between the cor pulmonale and the rheumatic heart disease groups. Similarly, there was no significant difference for the difference between atrial and ventricular pacing between the subjects with cor pulmonale and normal subjects or between the patients with rheumatic heart disease and normal subjects. The data in the normal subjects have been reported previously.¹¹ Correspondingly, the differences between ventricular and sequential atrioventricular pacing were not different for any of the three groups of patients, i.e. those with cor pulmonale, those with rheumatic heart disease and normal subjects. The same was true for the differences between the differences for atrial and sequential pacing for the three groups of subjects.

Discussion

These observations clearly demonstrate that the primary reason for the hemodynamic differences between atrial and

ventricular pacing lies in the absence of synchronized atrioventricular activity during ventricular pacing, since the indices during sequential atrioventricular pacing are only slightly less than those during atrial pacing, and the indices during atrial and sequential pacing are generally 20 per cent greater than those during ventricular pacing. Aberrant ventricular depolarization per se results in little decrease in cardiac indices. Part of the small decrement in flow during sequential atrioventricular pacing is probably caused by the shortened

P-R interval utilized of necessity in these sequential pacing studies. The artificial P-R interval in these latter studies must be employed to prevent atrioventricular conduction through the normal conduction pathways. It has been clearly shown in this study and in a related study¹¹ that the differences between atrial, ventricular and sequential atrioventricular pacing are similar for normal subjects and for cardiac patients. The failure of Benchimol and Diamond¹² to reach similar conclusions is probably due to the study of fewer patients and internal inconsistencies in their data¹³ previously discussed by us.¹¹

Summary

Comparison of the effects of atrial ventricular and sequential atrioventricular pacing in a group of patients with rheumatic heart disease and in a group with pulmonary emphysema has demonstrated that the absence of synchronized atrioventricular activity rather than aberrant ventricular depolarization is primarily responsible for the hemodynamic difference between atrial and ventricular pacing.

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The vectorcardiogram recorded with sponge electrodes

I. Culikoun Witham M.D.*

Angusta Ga

Increased use of vectorcardiography has created the dilemma of selecting one lead system from the many that are available. The exclusive adoption of the Frank system seems to be premature for its practicality does not necessarily compensate for serious theoretical objections. The most disturbing features are the sampling of the electrical field in a single transverse plane and from a small number of points. This design appears to account for the distortions of the λ and the Z components revealed by lead fields constructed from torso model experiments.¹ Grid electrodes—which integrate potentials from large areas of the chest—give a significantly better performance.^{2,4} Although several such systems have been designed there are no reports of their being tested clinically on a large scale.

The simplest of the family of grid systems has been suggested by Helm.³ Large sponge or gauze squares are used as electrodes in the λ and Z leads and appear to be acceptable grids. The theoretical foundation depends upon the torso model experiments of Frank.¹ It retains practical advantages of the Frank system e.g. ease of application and large voltages which minimize interference. It adds others. The care in positioning electrodes and in attaining very low skin resistances at numerous points is not so critical.⁵ The construction and maintenance of the input system are simple since new special electrodes can be cut

from sponge or gauze with a pair of scissors and no corrective resistor networks are necessary. Experience suggests that diagnostic features are qualitatively similar but not quantitatively interchangeable with those derived from studies with Frank's system. The following analysis of the sponge VCG in a normal population forms a basis for diagnostic evaluation and should encourage its clinical trial. Whether it will prove to have discriminatory superiority over that of the Frank system or others remains to be seen.

Patients recording measurements

One hundred thirty three normal Caucasians were selected for this study. The mean age was 24 years. About 90 per cent were hospital personnel. Heart disease was excluded by history, physical examination, x-ray film, hemogram and electrocardiogram. Cases of bundle branch block of any degree were excluded. ECGs with an r wave in Lead V_{3a} or Lead V_1 caused exclusion as possibly representing minimal right bundle branch block. The age and sex distribution are noted in Table I.

Vectorcardiograms were recorded in the frontal (FP), horizontal (HP) and right sagittal (SP) planes with strips of appropriate scalar λ , Y and Z leads on an Electronics for Medicine recorder. All patients were supine. Anterior and left axillary electrodes were composed of large squares of porous plastic sponge moist

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From the Medical Clinic of the College of Medicine, Department of Medical Clinic, Medical College of Georgia and Eugene Talmadge Memorial Hospital, Augusta, Ga.

Table 1 Age and sex distribution of patients

Age (yr)	Number (per cent)	Males (per cent)	Females (per cent)
16-20	24 (18)	4 (17)	20 (83)
21-25	60 (45)	30 (50)	30 (50)
26-30	35 (26)	25 (71)	10 (29)
31-34	14 (11)	5 (36)	9 (64)
Total	133 (100)	64 (48)	69 (52)

ened with saline. A concentrated solution appears to give more consistent results. Ordinary limb electrodes were used on the left leg, right arm, and a single position on the back.¹⁷ A suction electrode was used on the neck. Since only the QRS loop was to be studied, P and T loops were deleted electronically when desirable in order to clarify the initial forces. Loops were interrupted at 4 msec intervals. The size of the loop was adjusted so that the largest fitted comfortably within the frame. Loops in all planes were then recorded at this sensitivity. A 1 mV calibration was photographed on both channels.

Vector loops can be analyzed in numerous ways. The scheme followed herein is a modification of that developed by Mexican workers followed by Estes and is an attempt to quantitate morphologic features which have already proved to be diagnostically useful.⁶ The identification of the major spatial changes in direction allows one to describe most normal records with three vectors, each of which has three characteristics—time, direction, and voltage. Time as a descriptive variable is of course lost if used to define the vector itself. Loops redrawn from these three vectors more often mimic the distinctive morphology of the original than a similar number of points chosen at arbitrary time intervals. The vectors are also consistent with findings in studies of the activation sequence of the normal heart and their major anatomic contributors are mid-septum, left ventricular free wall, and posterolateral left ventricle and septum.¹⁸

A recent study indicates that such vectors generally have less variability than those identified at fixed time intervals.¹⁹

Although three vectors are usually ade-

quate to describe normal records, they do not always contain sufficient diagnostic information. In addition to the three major vectors (Q, R, and S), three others (20 msec V and S) have been utilized. These six plus rotation and time measurements currently constitute a satisfactory system of analysis and are illustrated in Fig. 1. They are defined as follows: A major directional change is considered to be at least 75 degrees in two or more planes. Q is the first major directional change within the first 20 msec. R is identified by the maximum leftward extent of the loop. S is the first major directional change after the R point. Twenty milliseconds is located by timing from the onset of the QRS loop in the plane in which the initial forces are best uncoded and in other planes by counting backward or forward from previously identified Q or R vector points. V is the maximum vector in each plane. S is a second major change in direction after the R point and of course the first after the S point as defined above. It was identified in the current series in only 13 per cent and data were therefore not utilized.

Spatial voltages were calculated by the use of a special nomogram (Fig. 2). The vector angles have been recorded in each plane according to the suggestion of Helm,¹ i.e. in a clockwise manner from 0 to 360 degrees. This convention is illustrated in Figs. 1 and 3.

An IBM 1620 unit was programmed to yield the following information about each of 41 variables: mean, standard deviation, test for normal distribution, frequency distribution plot, coefficient of variation, and coefficient of correlation for each variable against every other. The proper-

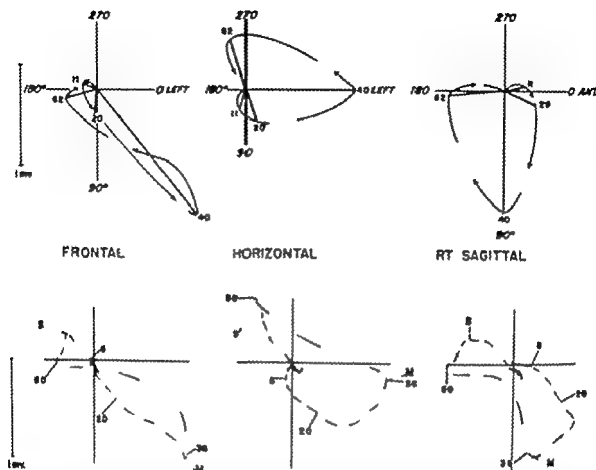


Fig 1 Top Loop—constructed from mean values of Q, R, and S vectors in Table I. The numbers 0, 20, 40, 60, 80 refer to the vector timing (in milliseconds) of these vectors. Heavy lines delineate the four vectors. A standard at extreme left. The convention of angular rotation clockwise from 0 to 360 degrees in each plane is used. Note that the right sagittal axis is used and the 0 degree is directly anterior. The frontal plane loop has been drawn to coincide with the most common rotation, i.e., figure-of-eight with counter-clockwise figure-eight. Bottom—Actual loops illustrating the six most important vectors. Interruptions are at 4 msec for all and the tail of the compass points in the direction of transcription. On each loop Q, 20, 40, and S point are marked by numbers corresponding to their timing from the beginning of the loop—i.e., at 0, 20, 40, 60, and 80 msec, respectively. The maximum (U) vector is about 1 msec earlier than R in the frontal and sagittal planes and coincides with it in the horizontal projection. The initial directional change (Q) is sharp—anterior extent is noted on the other two planes. The R point (maximum leftward) is sharply defined on the frontal and horizontal planes and by timing contour and vertical displacement on the sagittal. The first sharp slowing of inscription which begins here is well illustrated. On the lower limb 12 msec past the S point is another final directional change that occurs on the frontal and sagittal planes. This fits the definition of the S vector.

ties of each variable were then recalculated for males and females separately and the standard *t* test was applied to detect significant differences.

Results

The angles and voltages in each plane, spatial voltages and the timing of five vectors are included in Table II. The total

duration of the QRS loop, of the segment from the S point to the onset of the T wave (S loop) and of initial superior and inferior forces are noted. Also recorded are measurements of the R and S deflections of the three orthogonal leads and the sum of R in Σ and S in Σ . The means and standard deviations are noted in the conventional manner followed by a range in parentheses.

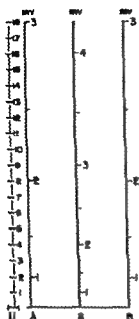


Fig. 3. Nomogram to solve the Pythagorean equation $S = \sqrt{X^2 + Y^2 + Z^2}$ where S is the partial voltage of a given vector and X , Y , and Z are the lower voltage expressed on horizontal, vertical and sagittal axes respectively. It is constructed as follows: A scale U of equally spaced units is drawn as a guide (centimeters on the original drawing). The numbers on scale X are square roots of those on scale U , $Y = \sqrt{U}$ where Y the number on X and U is the units on U . The numbers on scale I and B are found by the formula $X = \sqrt{U/2}$ and are identical. Calculations of course may be as detailed as desired. In one step two of the three variables X , Y , and Z may be found in one operation—e.g. if one measures the two-dimensional value of a vector in the horizontal plane, both horizontal (X) and sagittal (Z) components will be included. The vertical (Y) contribution to the partial vector may then be derived from loops in either the frontal or sagittal plane. If these two measurements are then marked on scales I and B and connected with a straight edge the partial voltage can be read on scale S .

This is two standard deviations above and below the mean if the distribution was adjudged to be acceptable normal. If not () the range represents 95.5 per cent of the 133 observations obtained by excluding the three highest and three lowest values.

The direction of transcription of the initial limb and the loop as a whole is described in Table III. Table IV presents the 25 statistically significant differences between males and females for the 41 χ^2 tests. Table V lists coefficients of cor-

relation and confidence limits of the relationships discussed in the text.

Fig. 3 illustrates the frequency distribution of angles and voltages of certain diagnostically important vectors.

Discussion

Comparison with Frank system. Strict comparison is not possible since available data for the Frank system are from various age and racial populations and the methods of measurement are not uniform.^{11,12} An impression may be gained from Fig. 4 although it must be remembered that the Frank data are abstracted from three different studies. Apparently the Helm system produces loops which are somewhat more vertically and anteriorly orientated voltages along the vertical axis (Y) are larger but the posterior extent (Z) is smaller. These differences fit Langner's finding that the Helm Y lead vector is larger than the Frank Y ¹⁴ and a comparison of major deflections of the Helm Z with those of Pipberger for the Frank Z which indicate a dominant posterior deflection for that system.¹⁵ Hugenholz unfortunately reports only angular measurements but the same trends are apparent.¹⁶ There is no clear choice between the systems in terms of variability of normal values based on the indirect comparisons available.

Characteristics of the normal vectorcardiogram. The availability of statistical correlations of each variable with every other permits a reasonably objective summary of the interrelationship of the principal vectors. The most useful points are discussed below and are based upon the correlations presented in Table V.

A. INITIAL VECTORS. The Q vector is consistently inferior and usually rightward but in the frontal plane the positions of Q and R (or maximum) vectors are largely interdependent. The angle between them is consistently wide (mean about 145 degrees). When the maximum vector is horizontal Q is usually inferior and to the right and when the maximum vector is vertical Q becomes superior and often slightly leftward. These relationships generally determine the direction of transcription of the different limb in the frontal plane—i.e. counterclockwise (CCW) with

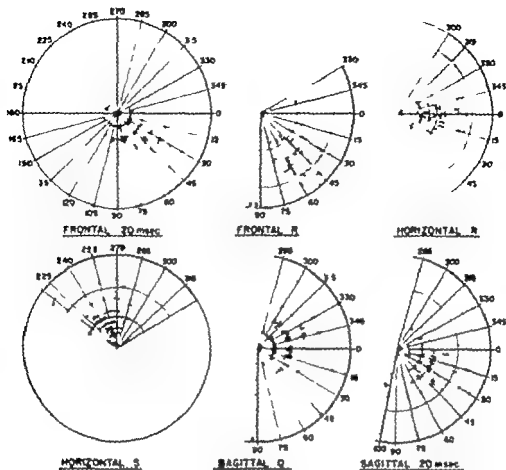
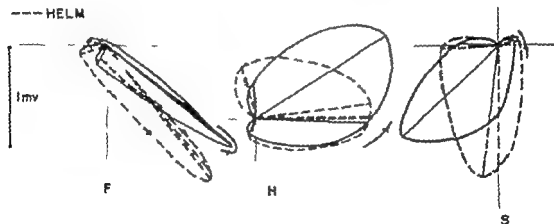


Fig. 3 Distribution of angles and voltages of some diagnostically important vectors. The centripetal scale in each diagram is in millivolt and the angular references follow those of Helm which are illustrated in Fig. 1.

— FRANK
 --- HELM



Voltage	Orthogonal Leads (mv)		Voltage	Maximum Vectors (mv)		Voltage	Spatial (mv)	
	Frank	Helm		Frank	Helm		Frank	Helm
R/S in X	1.2 ± .3	1.1 ± .2	FP	1.6 - 4	1.7 - 4	Q	1.7 - .09	2.2 ± .13
R/S in Y	1.0 ± .2	1.3 ± .1	HP	1.5 ± .4	1.1 ± .4	R	1.3 - 4	1.7 - .5
R/S in Z	.4 ± .9	.4 ± .5	SP	1.3 - 4	1.3 ± .4	S	.43 - .23	.60 - .29

Fig. 4 Superimposed loops for the Frank and Helm systems constructed from mean values. The four vectors indicated for each loop in each plane are respectively Q, R, S, and M. The source for the first three is the Frank loops as from McColl and for the M vector is an average of those reported by Draper¹ and Braxton.²

Table 11 Quantitative data on normal QRS loops—Helm system

	Q	Q msec	R	S	U
Amplitude (in green)					
RI	108 ± 69 (60-136)	91 ± 83 (13-300)	50 ± 14 (24-78)	164 ± 74 (17-311)	51 ± 21 (20-80)
IIP	108 ± 26 (43-143)	72 ± 34 (3-107)	0 ± 16 (135-40)	254 ± 24 (223-300)	354 ± 37 (210-25)
CI	118 ± 31 (295-60)	24 ± 37 (22-60)	90 ± 20 (37-116)	175 ± 33 (109-241)	97 ± 30 (37-219)
Amplitude (in m)					
RI	14 ± 09 (0-30)	24 ± 17 (03-60)	16 ± 4 (7-23)	32 ± 24 (05-90)	17 ± 4 (8-26)
IIP	20 ± 11 (12-50)	34 ± 13 (13-0)	11 ± 4 (3-19)	53 ± 26 (1-11)	11 ± 4 (4-18)
CI	21 ± 17 (12-51)	35 ± 15 (13-73)	12 ± 4 (4-21)	56 ± 28 (24-12)	13 ± 4 (6-21)
Amplitude	22 ± 13 (17-63)	38 ± 17 (13-76)	17 ± 5 (7-26)	60 ± 29 (6-14)	
Timing (msec)					
	11 ± 3 (5-18)	—	40 ± 3 (32-50)	62 ± 7 (47-76)	—
	Interior duration = 41 ± 10 (70-65)		Total QRS duration = 91 ± 13 (74-113)		
	Inter-1: superior duration = 12 ± 8 (0-27)		S loop duration = 28 ± 9 (14-49)		
Amplitude in orthogonal lead (mv)					
	R = 1.1 ± 4 (3.1-9)		S = 17 ± 17 (0-48)		
	R = 1.3 ± 5 (41-23)		S = 14 ± 19 (0-81)		
	R = 4.1 ± 22 (15-84)		S = 52 ± 20 (0-101)		
	R + S = 1.6 ± 5 (6-26)				

N.C. class 4 reference

Q 0 sec R 9 and U (in m) sec d 8 and 16 sec: IIP IIP SLP = F normal (normal) and a slight pd sec

Table III Rotation of efferent limb and QRS loops in a whole 133 cases (per cent)

Plane	CH	CCW	Figure of eight/index
Frontal			
I FF	29	63	8
QRS	21	14	59
Horizontal			
I FF	0	100	0
QRS	0	82	18
Sagittal			
I FF	98	<1	<1
QRS	92	<1	

I FF = I FF efferent limb QRS QRS loop
 (looks as if efferent limb is I FF) But as I FF is
 limb is determined by P-Q-T axis QRS loop will not
 be the same

horizontal loops and clockwise (CW) with vertical ones (Fig. 5)

The 20 msec vector is also normally inferior and usually inferior. Its distribution in the frontal and sagittal planes is seen in Fig. 3. The few superiorly oriented vectors with the highest voltages are from vertically oriented loops with CW efferent limbs. The maximum durations of initial superior forces were also seen in vertically oriented loops.

The rotation of the efferent limb of the loop is consistent in the horizontal plane (CCW) and in the sagittal plane (CW) (Table III). Spatial voltages of all vectors S excepted seem to vary together with high voltage Q and 20 msec vectors R and minimum vectors also tend to be large. The voltage of all vectors is also directly related to the timing. For example Q vectors of longer duration are generally found in loops with later R and S points and larger total QRS times such loops tend to have higher voltages.

Table IV Differences in values between sexes

Variable		Values (Mean \pm S.E.)	Females (Mean \pm S.E.)	t	p <
Time (msec)	Q vector	12.14 \pm 4.4	10.73 \pm 3.0	-2.620	0.1
	R vector	42.31 \pm 9.6	38.47 \pm 5.2	-4.985	0.01
	S vector	64.57 \pm 9.8	58.73 \pm 6.5	-5.174	0.01
	Total QRS	94.44 \pm 12.2	86.76 \pm 1.63	-5.725	0.01
Angle (deg, vec)	20 msec vector FI	125.30 \pm 12.10	61.7 \pm 7.04	-4.477	0.01
	III vector FI	41.45 \pm 1.84	55.07 \pm 1.72	3.311	0.01
	VI vector FI	43.51 \pm 3.05	58.18 \pm 1.53	4.381	0.01
	20 msec vector SI	11.56 \pm 3.06	34.85 \pm 5.19	3.802	0.01
Voltage (mV)	Q vector FI	16 \pm 0.13	12 \pm 0.08	-2.709	0.1
	III	22 \pm 0.14	18 \pm 0.12	-2.254	0.5
	SI	24 \pm 0.16	18 \pm 0.10	-3.251	0.1
	Spatial	25 \pm 0.18	19 \pm 0.12	-2.849	0.1
	R vector FI	1.79 \pm 0.54	1.46 \pm 0.17	-4.525	0.01
	III	1.30 \pm 0.16	0.86 \pm 0.34	7.686	0.01
	Spatial	1.83 \pm 0.36	1.48 \pm 0.50	-4.151	0.01
	VI vector FI	1.85 \pm 0.58	1.53 \pm 0.15	-4.217	0.01
	III	1.31 \pm 0.13	0.90 \pm 0.30	7.691	0.01
	S vector III	60 \pm 0.31	47 \pm 0.29	-2.981	0.1
	SI	67 \pm 0.35	50 \pm 0.32	-2.44	0.1
	Spatial	66 \pm 0.36	54 \pm 0.35	-2.360	0.5
	Orthogonal R	1.31 \pm 0.50	0.86 \pm 0.36	-7.319	0.01
	lead S _y	18 \pm 0.31	10 \pm 0.15	-2.360	0.5
	olting R	47 \pm 0.32	34 \pm 0.19	-1.596	0.01
	S	57 \pm 0.37	46 \pm 0.28	-3.010	0.1
	R + S	1.90 \pm 0.55	1.31 \pm 0.41	-8.487	0.01

MINI LOOP VECTORS The distribution of R vector angles is narrow in all planes and usually in close agreement with the M vector angle in the frontal and horizontal planes. An exception is with vertically oriented loops where the M vector is to the right of R in the frontal plane. The agreement is also less close in the sagittal plane where the maximum vector is frequently posterior to R. There is no valid correlation between the axes of the maximum or R vectors in the frontal plane and their counterparts in the horizontal plane. The voltages of mini loop vectors in the horizontal plane are of course greatly influenced by the spatial orientation of the loop. If it is elongated along the vertical axis it usually presents a smaller image in the horizontal plane.

Two VEC counterparts of ECG criteria for left ventricular hypertrophy are worthy of comment. The time of the R vector (counterpart of the intrinsoid deflection) generally correlates with the spatial R vector voltage. The voltage sum $R + S$ (counterpart of $R_1 + S_{11}$) also correlates with the spatial voltage of R and with the largest M vector (frontal plane).

In view of attempts to diagnose posterior

infarctions from the extent or duration of interior forces, the wide range of both are noteworthy.

TERMINAL VECTORS The last portions of the normal heart to be depolarized are probably the posterobasal portions of the left ventricle and septum.¹⁰ The direction of the S vector fits this site well. An obvious characteristic of most normal loops is the terminal slowing beginning near the S point which undoubtedly contributes to the change in direction which allows its identification. This presumably reflects a physiologic slowing of excitation possibly due to a priority of Purkinje fibers in this area.¹⁰ Its duration is highly variable and is apparently the largest single factor in determining the duration of the QRS loop (Fig. 6). Its duration is also closely related to the voltage of the S vector. When delay is pronounced the S vector may be the largest in the horizontal and sagittal planes.

It is apparent from Fig. 3 that a more precise evaluation of some vectors may be obtained by considering the interdependence of angle and voltage. For example, in S voltage of 1.0 mv and an angle of 230 degrees in the horizontal plane are within normal ranges, but the combination

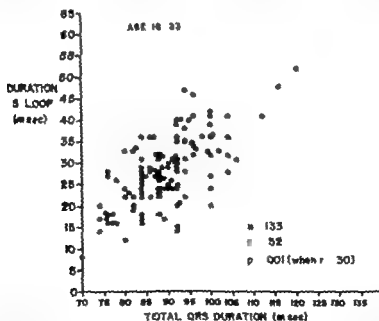


Fig. 6 Relation of duration of S loop to that of the QRS complex. The S loop is the segment from the S point to the beginning of the T loop (Fig. 1). Total QRS duration was plotted against 40 measured variables but this was by far the most significant correlation.

is not. Voltages of this magnitude are usually seen only with more directly posterior S vectors i.e. 255 to 275 degrees. This is a crude illustration of the largely unexplored potential of multidimensional analysis.¹⁴

A final sharp change in direction noted in 15 per cent of records has been called the S point identifying the S vector. It is slightly superior to S, closer to the null point by 8 to 24 msec and its spatial voltage is less. In the horizontal plane it is frequently indistinct being slightly to the right or left of the S vector. S vectors without these characteristics have been tentatively considered to be abnormal usually indicating either right ventricular hypertrophy or bundle branch block.

D. ROTATIONAL CHARACTERISTICS. In the frontal plane most loops are complex and seen on edge (Table III). Generally open loops with simple rotations have maximum vectors near the horizontal (CCW) or vertical (CW). The efferent limb however is usually CCW but its rotation is closely related to the position of the maximum vector in the frontal plane (Fig. 5).

In the horizontal plane the efferent limb was universally CCW but 16 per cent (24 cases) showed some later crossing. Most commonly this was minimal and at the S point (12 cases) or R point (1 case) where direction changes abruptly. The duration of the secondary loop in these 13 cases never exceeded 14 msec. Three other cases had open vertically oriented loops with M vectors in the frontal and sagittal planes of 85 ± 10 degrees and as one might expect small on edge loops with major crossings in the horizontal plane. One patient had unique narrow on edge loops with major crossovers in all three planes. Of particular interest were seven additional patients who had major secondary loops of 16 to 46 msec duration involving the S point. The S vector was unusually rightward (220 to 260 degrees in the horizontal plane) and was followed by a prominent S vector crossover posterior to the null point. These patients may well have had a minor grade of right bundle branch block although the ECG was unconvincing.

In the sagittal plane only two cases did not have clearly CW efferent limbs. In

both the whole loop was CCW due to normal Q and S vector directions associated with unusually high R vectors. The ECG revealed left axis deviation. In six cases there were brief secondary loops in the sagittal plane (less than 16 msec) involving the Q (1 case) R (3 cases) and S (2 cases) points. The previously mentioned patient with on edge loops in all planes was an additional unusual variant case.

E. DIFFERENCES BY SEX. Since sex distribution was approximately equal in this series normal values were recomputed for males and females. Table IV lists the statistically significant differences. Numerous values for voltage were higher in the male as previously reported.⁸ It is not surprising therefore that QRS duration and the timing of the major vectors also differ since these are closely related to voltages (Table V). Also the R and maximum vectors in the frontal plane were more rightward in the females and there were accompanying differences in distribution of the 20 msec vector along the vertical axis (frontal and sagittal planes). The differences however are unlikely to be due to sex alone since the groups could not be matched to equalize numerous other variables such as age, weight, etc.

Summary

A series of 133 normal young adults has been studied vectorcardiographically by the Helm lead system utilizing sponge electrodes. A quantitative system of analysis based principally upon loop morphology was used to describe the loops. Planar and spatial characteristics of five selected vector time intervals, rotation and major components of the scalar orthogonal leads are recorded. Measurements of diagnostic importance are stressed. A comparison has been made with data reported for the Frank system. In general there was similarity between planar angles for early and late vectors. The Helm mid loop vectors however appear to be more rightward and less posterior. Vertically oriented vectors have higher voltages and posterior ones have lower voltages. Males had significantly higher voltages and more horizontal loops than did the females. The features of normal loops by this system of recording

and their common variations are described in detail.

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The rheologic properties of low molecular weight dextrans Fact or fancy?

G M Collins B Sc MB BS FRCS

J Ladbroke B Med Sc Ch M FRCS FRACS

Sydney Australia

During the past 15 years an extraordinary range of properties has been attributed to low molecular weight dextrans (LMWD). This has resulted in their prescription for an equally wide range of clinical disorders in man.¹ We have had occasion to scrutinize the scientific evidence pertaining to some of the properties claimed for LMWD. A full critique would occupy a moderate sized monograph. We have contented ourselves with presenting an abbreviated but fairly fully documented review. Each section is headed by a commonly believed proposition which is then examined.

LMWD lowers blood viscosity

FOR After burns or crushing injuries in man and animals it has been shown that blood viscosity at all shear rates is raised and that treatment which includes the infusion of LMWD restores the viscosity toward the original value.²

AGAINST The fall in blood viscosity has always been associated with a reduction in hematocrit³⁻⁵ which in itself is known to reduce viscosity.⁶ Conventional 10 per cent preparations of LMWD have a relative viscosity considerably greater than that of plasma (unpublished observations) in almost all circumstances excepting plasma from patients with multiple myeloma¹⁴ in other words it is inherently improbable that LMWD will have a

specific viscosity lowering effect on whole blood. Indeed in studies in which LMWD has been added to blood *in vitro* provided that hematocrit is maintained constant or a correction is made for hemodilution all dextrans of molecular weight greater than 10 to 15 000 have regularly increased blood viscosity at all shear rates.^{4,6} Present evidence therefore suggests that if viscosity is lowered by adding LMWD to blood *in vivo* or *in vitro* it is because of simple hemodilution rather than from any intrinsic property of the dextran.

*LMWD inhibits the aggregation of red cells *in vitro**

FOR LMWD can diminish the high sedimentation rate of abnormal blood in proportion to the amount added whether it is added *in vivo* or *in vitro*.⁷⁻¹¹ It increases the electronegative charge on the surface of red cells and by implication increases their mutual repulsion.⁶

AGAINST No completely satisfactory objective measure of red cell aggregation has yet been evolved. The best available is probably the *in vitro* sedimentation rate but this is markedly affected by many factors which include plasma viscosity and specific gravity.^{12,13} Indeed high molecular weight dextrans or gum acacia in high concentration can produce a very low sedimentation rate even though marked

red cell aggregation is visible microscopically.¹⁴ Since 10 per cent LMWD also increases plasma viscosity and specific gravity it may well be that it lowers sedimentation rate for this reason rather than by a specific disaggregating action. A clear cut association between the surface charge on red cells and their state of aggregation has not been demonstrated for both high and low molecular weight dextrans render red cells more electro-negative.¹⁵ In man blood with a high sedimentation rate is often associated with a high fibrinogen concentration in the plasma.¹⁶⁻¹⁸ It appears that LMWD combines with this substance and indeed may visibly precipitate it.¹⁹ plasma fibrinogen content may be much reduced by the addition of LMWD.²⁰ In much of this work it has been assumed rather than demonstrated that the reduction of sedimentation rate by LMWD is associated with physical disaggregation of red cells. Indeed microscopic examination has shown that this may not be so.²¹

LMWD prevents sludging of blood in vivo
FOR The term sludging originated in the motor oil industry,²² and when applied to blood conjures up a vision of a sticky sediment of red cells obstructing the flow of blood. In disease states both gravitational separation of the red cells and plasma²³ and the apparent obstruction of small vessels by cellular aggregates^{24,25} have been observed to accompany a slowing of blood flow.²⁶ It is further suggested that these aggregates provide a physical obstruction to blood flow leading to anoxic damage and death.^{27-29,30,31}

LMWD has acquired a reputation as a flow promoting agent from reports of its ability to reverse sludging and its sequelae when these have been induced by thermal and mechanical trauma or by the infusion of high viscous dextran.^{32-35,36,37,38,39} This antisludging property of LMWD is usually equated with its apparent disaggregating effect in vitro.

AGAINST The pathologic significance of sludging itself is in some doubt.⁴⁰

There is considerable evidence to show that sludging occurs in healthy individuals either spontaneously or after the circulation has been slowed by vasoconstrictor agents or vascular obstruction and that

the process is completely and rapidly reversible.^{41,42,43,44,45,46}

There is a lack of consistency in the degree of sludging observed among vascular beds and among different vessels in the same tissue.^{47,48} In a more carefully controlled study the degree of sludging was not well correlated with the magnitude of the sedimentation rate nor was LMWD superior to solutions of dextrose or of conventional dextrans in reducing it.⁴⁹

Observations on the bulbar conjunctiva the region in which most human studies have been carried out take no account of the normal drainage of aqueous humor into conjunctival veins.⁵⁰ This might well create the impression of a separation of red cells from plasma.

Finally and most importantly it is not clear whether red cell sludging is the initiating factor^{47,51,52} in low blood flow states rather than the converse.^{53,54} It is entirely possible therefore that an apparent desludging action of LMWD is an indirect result of blood volume expansion and a direct result of the consequent changes in arterial pressure and vascular smooth muscle tone (q.v.)

LMWD promotes blood flow in small vessels

FOR The evidence is difficult to present briefly and difficult to dissociate from that which supports the desludging action of LMWD. Intravenous infusions of LMWD have been shown to increase blood flow in the forearm in both normal and abnormal human subjects.⁵⁵ Blood flow in the dog hind limb has been measured before and after the loss of blood and LMWD has been shown to be superior in restoring blood flow by comparison with isotonic saline or the lost blood itself.⁵⁶ In perfused dogs livers the reduction in flow caused by the addition of high molecular weight dextran has been partly reversed by the further addition of LMWD.⁵⁷

It is reported that the infusion of LMWD in postoperative shocked patients when compared with the infusion of equal volumes of whole blood causes a greater increase in central blood volume, central venous pressure and cardiac output with a lower peripheral resistance.⁵⁸ It is sug-

gested that this is due to an effective reduction in blood viscosity in small vessels.

AGAINST Blood flow in the human forearm is strikingly increased by a rise in central venous pressure as a reflex response¹¹ and LMWD is a potent short term blood volume increasing agent (qv). The greater magnitude of this latter action of LMWD by comparison with whole blood or isotonic saline may account for its superiority in restoring blood flow in the dog hind limb. Its effect on blood flow in the liver may be one of hemodilution; blood plasma was not used as a control.

The reported superiority of LMWD as a flow promoting agent in shocked patients neglects its greater blood volume expanding effect by comparison with the control infusions. The greater rise in central venous pressure and central blood volume would be expected to cause a reflex reduction in tone in muscle resistance vessels^{12,13} the fall in peripheral resistance can be explained in this way rather than by a lowering of viscosity. Indeed in a similar study of LMWD in normal and postoperative subjects it is concluded that LMWD has the same hemodynamic action as other blood volume expanders.¹⁴ This has been confirmed by the demonstration of an identity of effect of LMWD and conventional dextrans in patients with severe arterial insufficiency in the lower limbs.¹⁵

LMWD acts as a blood volume expander

FOR When LMWD is infused as a 10 per cent solution it appears that a disproportionately great expansion of blood volume occurs, i.e. the increase in blood volume is 50 to 100 per cent greater than the volume of LMWD infused¹⁶ presumably because of an oncotic effect. Its chief advantage as a blood volume expander is that it is cheaper and can be more readily available than whole blood plasma or albumin and it avoids the gross aggregation of red cells which dextrans of higher molecular weight cause.

AGAINST The rapid renal excretion of the smaller molecules restores blood volume to control levels within 3 to 6 hours after a single infusion of LMWD^{17,18} although this by no means renders it valueless. However the commercial preparations

of LMWD contain a proportion of dextrans of molecular weight 70 to 80 000¹⁹. These are destroyed only very slowly probably by metabolic pathways.²⁰ Thus large or long continued infusions of LMWD should result in an ever increasing plasma concentration of those fractions with the very adverse properties which LMWD was designed to avoid.¹²

LMWD acts as an osmotic diuretic

FOR The smaller molecules in LMWD are rapidly excreted by the kidney. In normal man 70 to 80 per cent of the fractions below 40 000 mean molecular weight can be recovered from the urine within 12 hours.²¹

AGAINST A careful study in dogs shows that although LMWD may be excreted in extremely concentrated form (up to 50 per cent) it has a minimal osmotic diuretic action in conventional dosage.²² Indeed the resultant viscosity of the urine may be such as to limit the flow of urine through the renal tubules.

Summary

We are forced to the conclusion that none of the new and extraordinary rheologic properties which have sometimes been claimed for low molecular weight dextrans have yet been proved to be genuine. However it does seem that they are comparatively safe short term blood volume expanders.

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An evaluation of computed stroke volume in man

William B Jones MD*

Richard O Russell Jr MD

Dallas H Dalton Jr MD

Birmingham Ala

A method of obtaining an approximation of the aortic blood velocity from the aortic pressure pulse has been previously reported from this laboratory.^{1,2} The method consists of obtaining a continuous solution of a simplification of the Navier Stokes equation (the general equation describing fluid dynamics) using the aortic pressure pulse as the input signal to an analogue circuit. The simplified equation is as follows:

$$\partial P/\partial t + 1/r = p \frac{du}{dt} + au \quad (1)$$

P is aortic pressure, t is time, p is a constant for density, r is a constant for the rate of pulse transmission, u is the blood velocity, and a is a blood friction constant. The general method has been previously discussed by the authors and others.^{1,2}

Reasonable validation has been established in dogs by comparison of the derived velocity curves with curves obtained from an electromagnetic flowmeter.² The previous comparison revealed a correlation coefficient of 0.93 when the two independent flow curves were used as estimates of stroke volume.

The method would appear to have its major usefulness in studies of human cardiovascular dynamics. Since several

assumptions and simplifications are involved in the method further validation of the technique is applied to man as indicated. This paper reports a comparison of cardiac outputs derived from the computed aortic velocity curves and results obtained by other methods i.e. dye dilution and Fick determinations.

Methods

The comparison data were obtained from two studies recently completed in the cardiac catheterization laboratory. The first was a study on normal volunteers to determine the effect of eating on hemodynamics at rest and exercise. This has been previously reported.³ Ten subjects were studied in this group. For each study multiple determinations of cardiac output were obtained by the dye dilution technique with indocyanine green. The derived flow curves were recorded simultaneously as will be outlined below.

Other data were obtained from exercise studies on 32 patients with known or suspected heart disease. This was done as part of a hemodynamic and anatomic evaluation. In these patients a resting Fick determination was made. Then each subject exercised for 4 minutes and a repeat determination was made during the fourth minute.

From the Department of Medicine, Medical College of Alabama and the Medical Service, Veterans Administration Hospital, Birmingham, Ala.

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Address: Medical College of Alabama, 1919 Seventh Ave South, Birmingham, AL 35233.

In all subjects a No 3 Teflon catheter was introduced into a brachial artery by the percutaneous technique and advanced until the tip was in the ascending aorta. The pressure was sensed with a Statham P23D manometer. The catheters were optimally damped with a mechanical compression device. The catheter manometer system has been found to be linear to 25 cycles per second.

A multichannel oscilloscopic recorder was used.⁶ The first time derivative of the aortic pressure pulse was obtained with a simple RC differentiating circuit. The output from this circuit was modified by a computer circuit designed to give a continuous solution of the modified Navier Stokes equation. The computer circuit used is similar to that previously described by Fry and co workers.⁶ The output from this circuit is considered to have an output proportional to the velocity of flow in the ascending aorta and is recorded as a velocity curve. In addition a continuous integration of the velocity curve was obtained by means of a rectifying integrator which triggers from the

R wave of the electrocardiogram.⁶ The original aortic pressure signal and its various modifications are illustrated in Fig 1.

The computer circuit used has a variable adjustment to compensate for variations in inertia and friction. Prior to each study this adjustment was set so that the derived velocity tracing returned to its base line synchronously with the aortic incisure. Once this setting had been made a tracing was obtained prior to and immediately after a determination of cardiac output by either the Fick or the dye dilution method. No changes in the setting were made during the course of the study.

The assumption is made that the size of the ascending aorta is relatively constant so that the velocity curve obtained in this area would have the same shape as a volume flow curve. Therefore the height at the end of systole of the integrated velocity curve was measured and considered to be proportional to stroke volume. Such curves were obtained before and after each determination of cardiac output by the Fick or the dye dilution method. An average figure from at least five cycles

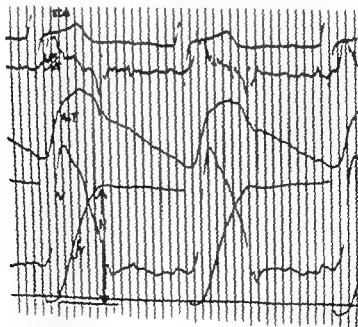


Fig 1 A representative tracing showing the ECG, the first time derivative of the aortic pressure, the blood velocity curve (V) and the integral of the velocity curve ($\int V$). The measurement H is taken as being proportional to stroke volume.

was obtained in each situation for the initial resting determinations the average figure obtained from the integrated velocity curve was multiplied by heart rate to obtain a figure proportional to cardiac output. The determined cardiac output was divided by this figure to provide a calibration constant. Subsequent comparison points were obtained by multiplying the heart rate by the average height of the integrated velocity curve by the calibration constant.

In the physiologic studies to determine the effect of meals the subject exercised twice and at least one and occasionally two dye dilution outputs were determined during each period of exercise. In addition several comparison points were obtainable during the rest period between the two exercise studies. For the clinical studies one resting determination was made and one exercise determination.

Results

A total of 73 comparison points has been obtained. 42 from the 10 subjects in the study concerning the effect of meals and

31 from 31 patients undergoing exercise as part of catheterization. These ranged from essentially normal subjects to patients with severe mitral, aortic or myocardial disease. Patients with severe aortic insufficiency or with shunts were excluded. The patients with aortic insufficiency were excluded because of the difficulty in measuring the backflow by means of the velocity curves. Patients with shunts were excluded because of the difficulties in determining cardiac outputs by either the dye dilutions or the Fick technique. The patient studies are consecutive live subjects were excluded from the calibration because of inability to duplicate Van Slyke analysis or failure to follow the exercise protocol.

Fig. 2 is a plot of the cardiac output determined from the derived velocity curves against Fick or dye dilution outputs. A correlation coefficient of 0.90 was obtained. The regression line is described by $y = -1.09 + 1.23x$. The standard deviation is 1.85 L. per minute. As can be seen the scatter is more apparent at the higher output levels.

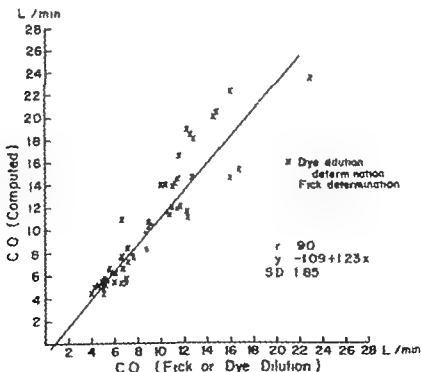


Fig. 2 A comparison of cardiac outputs as determined by dye-dilution or Fick method with that computed from velocity tracings obtained by the time derivative method.

When the points of comparison with the dye dilution outputs alone are considered the correlation coefficient = 0.92. It is 0.88 for the Fick determinations alone.

Discussion

The findings in man are in agreement with those previously made in dogs and confirm that the method of obtaining an approximation of the aortic blood velocity appears to be acceptably accurate. The method exaggerates the stroke volumes at the higher levels giving a regression line with a steeper slope than the identity line. This can be corrected to some extent by using the regression equation to modify the derived cardiac output.

From Fig. 2 it is apparent that there is moderate scatter particularly at the higher cardiac outputs. Part of this scatter can be attributed to inaccuracies of the Fick and dye dilution techniques during exercise. In addition an error in the initial

cardiac output determination used for calibration would result in a consistent error in all subsequent computed values. The average percentage of error is essentially constant for all cardiac outputs measured.

The major theoretical assumption in the use of the time derivative is that the rate of pulse transmission (s in Equation 1) is the same for all relevant frequencies in the ascending aorta. If this is assumed then the time derivative and the spatial derivative of pressure have the same form and s serves as a calibration factor. No direct measurements referable to this have been made in the ascending aorta. However available evidence suggests that flow impedance varies only minimally with frequency in the ascending aorta.^{7,8} By extension this suggests that s is relatively constant in this area.

Greenfield and Fry recently reported a surprising validation of the time deriva-

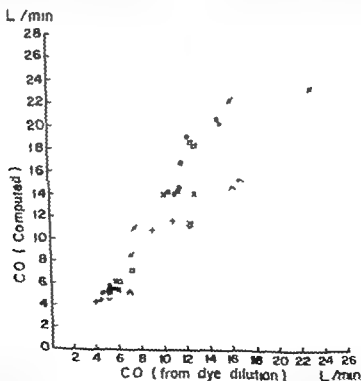


Fig. 2. A display of the comparison of cardiac outputs determined by dye dilution with that computed from the derived aortic velocity tracing in subjects who had multiple determinations at rest and during exercise. The comparison points from single and multiple dye dilution are differentiated by symbol. Calibration of the computed values is obtained from an initial cardiac output value. The calibration lines are not plotted.

tive technique in the descending aorta. They confirm the empirical usefulness of the method but challenge the theoretical assumptions on the basis of discrepancies between the experimental time constant (the ratio of resistance and inductance terms) and the predicted time constant. These discrepancies are not surprising in the descending aorta where the flow impedance has been simply demonstrated to be frequency dependent.¹⁰ However their conclusions are not necessarily applicable to the ascending aorta. In any case the usefulness of the method is determined by experimental validation irrespective of theoretical background.

In application it would appear to be preferable in all studies to obtain periodic determinations of output by either the dye or Fick method so as to construct an individual regression line in each subject. This would permit a beat by beat study of output and provide detail of the changes in cardiac output determinations obtained by the standard methods. All comparison points exclusive of the initial one used for calibration are shown from the subjects in whom multiple determinations were made (fig 3). The subjects are identified by symbol. It can be seen that the correlation in each individual subject is better than that of all subjects considered together.

It is apparent that the change in the heart rate during exercise is a major determinant of exercising cardiac index. In most subjects the stroke volume changes very little with exercise so that the major variable is heart rate. Therefore it is conceivable that the correlation coefficient of 0.90 as reported is primarily a correlation of heart rate and cardiac output. To test this hypothesis it was assumed that the resting stroke volume was a constant and that all subsequent variation was due to change in heart rate. The correlation of Fick or dye cardiac output with an output approximation from heart rate multiplied by resting stroke volume is 0.74. It is apparent that stroke volume as determined by the method reported in this paper improves the correlation considerably.

The technique appears to have considerable potential as an adjunct to the

standard methods of determining cardiac output in that it permits assessment of beat by beat changes and rapid changes. It has the advantage of requiring only a single lumen catheter in the ascending aorta. However accurately obtained properly damped aortic pressure curves are a necessity if valid curves are to be secured.

Summary

Data for validation in man of a method for determining continuous cardiac output are presented. Seventy three points of comparison between a Fick or dye dilution value and a value computed from the pressure pulse in the ascending aorta give a correlation coefficient of 0.90. The method described is based on a continuous solution of the Navier Stokes equation with the first time derivative of the aortic pressure used as the input signal.

We wish to express appreciation to Dr Donald A McDonald for criticism and advice.

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Five-year follow-up study of cases suggestive of acute myocarditis

Elias Bengtsson M.D.*

Berndt Lamberger M.D.

Stockholm Sweden

The findings in various autopsy series¹⁶⁻¹⁷ indicate that acute myocarditis frequently attends acute infectious diseases. In clinical practice however the diagnosis is more rare. The diagnostic criteria often based solely upon electrocardiographic findings are not always unequivocal. In earlier investigations¹⁸⁻¹⁹ of normal individuals and individuals suspected of having acute myocarditis an attempt was made to enhance the electrocardiographic diagnosis coordinate various clinical findings determine the physical working capacity as a function of the stroke volume of the heart and apply a more fully developed method for determination of the heart volume. According to the criteria applied in these investigations the physical working capacity of patients with myocarditis was reduced to some extent the reduction being particularly conspicuous in relation to heart volume which was frequently enlarged.

The prognosis of acute myocarditis has always been regarded as being favorable (except in cases of diphtheria and trypanosomiasis) although no major series has been followed over long periods. In order to shed further light on this problem we followed for 5 years after the onset a number of patients from the previous

series of cases of acute myocarditis. The findings were compared with those for cases in which the diagnosis of myocarditis had been doubtful and with those obtained in a control series which 5 years earlier had shown no signs of cardiac involvement. Examinations and methods were the same as before.

Material

During the period 1950 through 1955 a large number of patients suffering from acute infectious diseases was examined electrocardiographically with standard leads usually at intervals of 1 week. As a rule both chest and unipolar extremity leads were taken whenever the standard leads revealed manifest or suspected changes. Thus 2310 patients were examined with chest leads. In most cases pathologic changes were attributed to extracardiac causes but in 201 cases they were considered to be suggestive of acute myocarditis. The latter cases were subjected to electrocardiographic and other studies which along with the principles of selection have already been reported.

Briefly summarized the repeated electrocardiographic examinations did not reveal stationary changes and the changes were not attributed to tachycardia congenital or previously acquired heart dis-

* From the Department of Medicine, Högskolan, Stockholm, Sweden.

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Address reprint requests to Dr. Bengtsson, Stockholm, Sweden.

case or cardiovascular. Discarded were cases in which the ECG changes could be duplicated or eliminated by certain agents with a neurovegetative action as well as cases with concomitant electrolyte disturbances and those in which certain other extracardiac factors might have influenced the ECG. Also excluded were cases with certain transient disturbances of rhythm and conduction not associated with other electrocardiographic changes or other clinical symptoms.

It was planned to follow up during the years 1955 through 1959 those patients who had been hospitalized during the period 1950-1954. This series totaled 130 cases. Excluded from the follow up investigation however were all patients over the age of 49, patients with paralysis, 15 patients who had moved from Stockholm and 3 who could not be traced. No other selection was practiced and the follow up study thus comprised a total of 90 cases which 5 years earlier had been chosen as suggestive of acute myocarditis.

The previous investigations had included 61 cases in which the diagnosis of myocarditis was doubtful. Twenty six of these patients who were under 50 years of

age and free of paralysis but otherwise unselected underwent follow up examinations.

In another previous investigation ⁴ electrocardiograms (ECGs) had been recorded and the working capacity determined in 63 patients hospitalized for various infectious diseases; the examinations had revealed no signs of cardiac involvement either during hospitalization or after 1 month of convalescence. Thirty four cases were taken from this series on the same basis as before and used as a follow up control group.

The present investigation is concerned chiefly with the 90 cases in the first group. At the onset 5 years earlier the primary acute infectious disease in 50 per cent of the cases had been due to hemolytic streptococci. The distribution of diseases in the group is shown in Table I. The subgroup comprising 12 cases of miscellaneous infectious diseases was made up as follows: 2 cases of infectious hepatitis, 2 of bacillary dysentery, 2 of pertussis, 3 of obscure fever and 1 each of mononucleosis, diphtheria and measles.

Streptococcal diseases also accounted for 13 (50 per cent) of the 26 dubious

Table I. Subjective symptoms and phonocardiographic findings in cases suggestive of myocarditis

	Total series		Number of patients with subjective symptoms	Systolic murmurs		
	Number	Per cent		High frequency	Pansystolic	Mid systolic
Rheumatic fever	18	20	3	6	7	2
Scarlet fever	20	22	4	8	2	7
Other streptococcal diseases	6	7	0	0	0	0
Nonhemolytic streptococci	9	10	4	2	0	0
Acute meningitis	16	18	3	1	1	0
Poliomyelitis	4	4	2	0	0	0
Pneumonia	5	6	1	1	1	0
Miscellaneous infectious diseases	12	13	6	1	1	0
Total number of cases	90		23	19	7	4

cases in the second group including 3 of polyarthritia (but none of rheumatic fever according to Jones criteria) Of the other 13 cases there were 5 of upper respiratory infections and pneumonia, 2 of poliomyelitis, 2 of aseptic meningitis and 4 of paratyphoid fever. Aside from a greater proportion of cases of infectious hepatitis and the absence of rheumatic fever the acute infectious diseases showed much the same distribution in the control group.

During the 5 years after the hospitalization no one in these series had been hospitalized for any infectious disease nor personally ill at home from any similar disease. At the time of the follow up examination all were healthy and no one had suffered from any respiratory or other infectious disease of any consequence during the previous 4 weeks.

Methods

The methods applied for electrocardiographic examination at rest³ and during exercise⁴ and for determination of the physical working capacity and heart volume⁵ were identical with those used in the investigations 5 years earlier. In the orthostatic tests ECG's were recorded after the subjects had been in the erect position for 10 minutes. Arrhythmic data were annotated in accordance with the previously used questionnaire.

Electrocardiograms were recorded from CR leads and during exercise from CH leads (chest lead).⁴ In the exercise tests ECG's as well as heart rate and respiration rate were recorded at 2 minute intervals. The physical working capacity was determined by bicycle ergometer tests at the load coinciding with a heart rate of 140 beats per minute under steady state conditions.⁵ Heart volume was determined roentgenologically by the method of Kjellberg, Lönroth, Radhe and Sjöstrand.^{6,7}

Electrocardiograms were evaluated on the basis of previously reported normal values⁴ heart volumes and working capacities on the basis of the regression lines with 95 and 99 per cent limits reported for normal series.⁸

Results

Subjective symptoms (Table I) All subjective distress recorded in the following

was stated to have arisen at the time of or shortly after hospitalization 5 years earlier.

Fatigue was reported without descriptive detail by 9 patients (10 per cent) only 2 of whom mentioned no other symptoms. Dyspnea or other physical impairment that could be satisfactorily defined was reported by 12 patients. Precordial pain symptoms of oppression or arrhythmia were reported by 18 patients (20 per cent) 6 of whom made no reference to other symptoms.

The distribution of symptoms by type of disease is shown in Table I. The groups with rheumatic fever, scarlet fever and aseptic meningitis had roughly the same incidence of symptoms (approximately 20 per cent) but in the group with miscellaneous diseases every second patient had symptoms of some type.

At the time of examination 4 of the patients with subjective distress had sedimentation rates of 20 to 30 mm and in 3 of these 4 the antistreptolysin titers were elevated to 800, 500 and 640 units per milliliter. None of them however reported any aggravation of the subjective symptoms.

Out of the total of 23 patients only 2 exhibited abnormalities on the resting ECG's. 7 had electrocardiographic abnormalities on the orthostatic tests including 3 with no other ECG changes. The exercise ECG's were abnormal in 10 patients only one of whom had shown abnormalities on the resting ECG.

In 8 of the 23 patients the physical working capacity was abnormally low (falling outside the 95 per cent limit) in relation to body weight in 11 it was abnormally low in relation to heart volume. In 8 of these patients the values were abnormal in relation to one but not to both of these factors. Six patients had a normal working capacity in relation to each of the two factors. Heart volume was abnormally large in relation to body weight in 7 patients but normal in 16.

Phonocardiographic findings (Table I) The physical findings were consistent with the phonocardiographic data. Analysis of phonocardiograms from the entire series revealed not a single patient with diastolic murmurs such murmurs as were noted

were largely referable to the groups with rheumatic fever and scarlet fever. The other groups included only occasional cases of murmurs. The incidences were approximately equal—about 60 per cent—for the rheumatic fever and the scarlet fever groups.

As for systolic murmurs only the high frequency, the pansystolic and the mid systolic were recorded. In the total series

the respective incidences of these murmurs were 21.1, 7.8 and 4.4 per cent. In the combined rheumatic fever and scarlet fever groups high frequency murmurs were noted in 36.9 per cent, pansystolic and mid systolic murmurs each in 10.5 per cent.

Of the 21 patients with murmurs 15 had abnormal ECGs, roughly one half had low working capacities and approximately one fourth had enlarged heart volumes.

Electrocardiographic findings (Tables II and III). Abnormalities were noted on the resting ECGs of 21 patients, approximately one half of whom had normal exercise and orthostatic ECGs. Ten patients had abnormal ECGs on the orthostatic test but in 5 of them the resting and exercise ECGs were normal. Twenty eight showed electrocardiographic abnormalities on the exercise test but 16 of these had normal ECGs at rest and on the orthostatic test.

The most common abnormalities were those in the terminal segment, disturbances in rhythm being next in order and conduction disturbances comparatively rare.

Atrioventricular conduction disturbances were observed chiefly in cases of rheumatic fever, as were intraventricular conduction abnormalities. Disturbances in rhythm

Table II Distribution of abnormal electrocardiograms

Abnormalities on	Number of cases
Resting ECGs	30
Orthostatic ECGs	5
Exercise ECGs	16
Resting + orthostatic ECGs	0
Resting + exercise ECGs	8
Orthostatic + exercise ECGs	2
Resting + orthostatic + exercise ECGs	3
Total number of cases	44

Working capacity: 4 heart volume increments stable in 3 patients.

WV: long capacity and heart volume stable in 1 patient.

Table III Types of electrocardiographic abnormalities in various infectious diseases

	Total cases	Rhythm disturbances			Atrioventricular conduction disturbances			S-T segment and T wave changes			Total abnormal
		Resting	Ortho	Exercise	Resting	Ortho	Exercise	Resting	Ortho	Exercise	
Rheumatic fever	18				2	1	1	1	1	3	8
Scarlet fever	20	2		1	1			3	3		12
Other streptococcal diseases	6							1		1	2
Nonstreptococcal tonsillitis	9							2	1	2	5
Aseptic meningitis	16	1		2				4	1	10	18
Polioarthritis	4	1	2	2				2			7
Pneumonia	5			2							2
Miscellaneous infectious diseases	12			3				2	1		6
Number of changes	90	4	2	10	3	1	1	15	7	18	

on the other hand were usually associated with cases of nonstreptococcal disease notably poliomyelitis and pneumonia. Abnormalities of the terminal segment were recorded in all disease groups with the highest incidence in cases of aseptic meningitis and the lowest in cases of rheumatic fever.

Disturbances in rhythm first evidenced on the exercise ECGs were largely referable to the groups with nonstreptococcal diseases. Such abnormalities of the terminal segment as were first manifest on the exercise ECGs were most commonly associated with streptococcal diseases but were also noted in a number of cases of aseptic meningitis.

Disturbances in rhythm on orthostatic tests were confined to cases of poliomyelitis whereas abnormalities of the ST segment and T wave on such tests were recorded in the majority of other groups although most commonly in cases of scarlet fever.

Abnormal electrocardiograms in relation to reduced working capacity and abnormally large heart volume. Cases in which there was an abnormal ECG were divided into two groups: one with a streptococcal etiology and the other with a nonstreptococcal etiology. For the streptococcal disease group the working capacity was abnormally low in 5 patients and normal in 8 whereas the heart volume was abnormally large in 2 but normal in 11. For the other group the working capacity was impaired in 12 patients and normal in 11; the heart volume was abnormally large in 6 and normal in 17. Among the patients with aseptic meningitis in the nonstreptococcal group abnormally low and normal working capacities as well as abnormally large and normal heart volumes showed approximately equal distributions (about 5 or 6 cases in each of the categories).

Electrocardiographic abnormalities at different examinations in relation to working capacity and heart volume (Table IV). In 17 cases in which the resting ECG was abnormal both the physical working capacity and the heart volume were studied. The working capacity evaluated in relation to heart volume was abnormally low in 11 of the 17 patients evaluated in

relation to body weight; it was abnormally low in 6 and within the normal range in 11. Only 3 of the 17 patients had enlarged heart volumes.

In addition to these 17 patients there were 3 in whom right bundle branch block was manifest on the resting ECGs (but not on the exercise ECGs). Each of the 3 had a normal working capacity and heart volume.

Of 9 patients with electrocardiographic abnormalities on the orthostatic tests 4 had reduced working capacities and 1 had an abnormally large heart volume. All patients with abnormal working capacity and/or heart volume were referable to the nonstreptococcal disease group.

Of 27 patients with abnormal exercise ECGs 7 had abnormally low working capacities in relation to body weight and 13 in relation to heart volume. Nine had abnormally large heart volumes in relation to body weight.

Working capacity (Table V). Reduced working capacities were no more common in patients with streptococcal diseases than in the others. In the total series the physical working capacity—considered in relation to either body weight or heart volume—was reduced to values below the 95 per cent limits in 41 per cent of the patients. The working capacity was abnormally low solely in relation to body weight or age in 15 patients, solely in relation to heart volume in 12, and in relation to both heart volume and age or body weight in 17.

The impairment of working capacity moreover was more pronounced in relation to heart volume than to body weight. In the former context 17 of 29 cases fell below the 99 per cent limits; in the latter only 8 of 23.

Of the 34 patients with low working capacities 20 had abnormal ECGs and 13 had abnormally large heart volumes.

Heart volume (Table VI). Abnormally large heart volumes in relation to body weight were noted in one fifth of the cases. Approximately 50 per cent of these cases exceeded the 95 per cent upper limit of the previously determined normal range and the other 50 per cent exceeded the 99 per cent limit. Of the latter 50 per cent the majority were cases of rheumatic fever.

Table IV Working capacity and heart volume in patients with abnormal electrocardiograms

Abnormalities of ECG	Number of cases	Working capacity in relation to				Heart volume in relation to body weight	
		Body weight		Heart volume		Large	Normal
		Low	Normal	Low	Normal		
Reversing ECG	17	0	11	11	6	3	14
Orthostatic ECG	9	4	5	4	5	1	8
Fixed ECG	27		20	13	14	9	18
Total	53	14	36	28	25	13	40

Table V Working capacity in relation to body weight or age and heart volume in various infectious diseases

Infectious diseases	Total number of cases	Working capacity in relation to								Abnormally low working capacity	
		Body weight or age					Heart volume			Total number of cases	Per cent
		Below		Not exam- ined	Below		Nor- mal	Not exam- ined			
		50 per cent or less	99 per cent or less		95 per cent or less	99 per cent or less					
Rheumatism	18	2	1	14	1	0	4	13	1	6	33
Scarlet fever	20	5	1	13	1	4	1	12	1	8	40
Other streptococcal	6	1	1	4	0	0	1	4	1	1	
Whooping cough	2	4	0	5	0	3	0	6	0	5	56
Acute epiglottitis	16	1	2	13	0	2	4	10	0	6	38
Polymyositis	4	0	1	0	3	0	1	0	3	1	
Peritonitis	5	0	0	5	0	0	0	5	0	0	0
Mucocutaneous infectious diseases	12	2	2	7	1	3	4	4	1	7	64
Total number of cases	90	15	8	61	6	12	17	54	7	31	41

Of the 17 patients with abnormally large heart volumes approximately one half had abnormal ECGs and 13 had abnormally low working capacities.

Findings in patients with suspected cardiac involvement on admission to hospital (dubious myocarditis group) (Table VII). At the time of hospitalization 3 years earlier

the ECGs of some patients had not been unequivocally abnormal according to the criteria applied⁷ and those of others had been interpreted as being dubious. The patients were subjected to identical examinations at the time of the follow up and the findings are recorded in Table VII in which the cases are grouped with re-

Table VI Heart volume in various infectious diseases

	Total number of cases	Heart volume in relation to body weight			(abnormally large heart volume)		
		Exceeding		Normal	Not examined	Number of cases	Per cent
		95 per cent limit	99 per cent limit				
Rheumatic fever	11	1	4	12	1	5	28
Scarlet fever	70	2	0	17	1	2	10
Other streptococcal diseases	6	0	1	3	1	1	
Nonstreptococcal tonsillitis	9	1	0	8	0	1	
Aseptic meningitis	16	2	3	11	0	5	31
Prioniasis	4	0	0	2	2	0	
Pneumonia	5	1	0	4	0	1	
Miscellaneous infectious disease	12	1	1	10	0	2	17
Total number of cases	90	8	9	67	5	17	20

Table VII Follow up findings in the dubious cases of myocarditis

	Streptococcal diseases (23)	Nonstreptococcal diseases (13)	Total number (36)	Per cent of total number
Subjective symptoms	5	2	7	27
Elevated antistreptolysin titer	2	2	4	13
Abnormal PCG	5	0	5	19
Abnormal resting ECG	1	2	3	17
Abnormal orthostatic ECG	5	7	7	27
Abnormal exercise ECG	3	4	7	27
Total number of patients with abnormal PCG	7	6	13	50
Low working capacity	8	4	12	46
Enlarged heart volume	4	1	5	19

spect to diseases of streptococcal or other etiology.

Findings in patients with no signs of cardiac involvement on admission to hospital (Control Group) (Table VIII). Of the 34 patients comprising this group 16 had had a years earlier infectious diseases due to hemolytic streptococci and 18 had had infectious diseases of other etiology.

At follow up examination 2 patients reported subjective symptoms: one of them fatigue and the other dizziness and precordial pain. The latter patient was a 16-year-old girl who had suffered from scarlet fever. Her resting ECG showed partial right bundle branch block, the

orthostatic ECG certain abnormalities, the exercise ECG a diphasic T at 4 minutes after exercise, the phonocardiogram a low frequency early systolic murmur of low amplitude and the functional test a working capacity below the 99 per cent limit of a normal series.

The second of the two patients with abnormal exercise ECGs exhibited a negative T wave in the apical lead during exercise and an isoelectric T wave in the same lead after exercise. This patient, a 15-year-old boy, had a somewhat low blood pressure of 105/60 mm Hg, but in all other respects the findings were normal.

Comparison of cases without cases with

Table VIII Incidence of signs and symptoms in three groups examined 5 years earlier: patients without signs of cardiac involvement (controls), patients with dubious myocarditis and patients with presumptive myocarditis

Findings	Controls (34)		Dubious myocarditis (26)		Presumptive myocarditis (60)	
	Number	Per cent	Number	Per cent	Number	Per cent
Subjective symptoms	3		1	37	23	24
Elevated antistreptolysin titer and/or ESR	8	23	4	15	25	28
Abnormal PEG findings	1		5	19	21	23
Abnormal resting ECG	0		3	17	17	19
Abnormal orthostatic ECG	4	12	7	27	9	10
Abnormal exercise ECG	2		7	27	27	30
(Total with ECG changes)	5	14	13	50	44	49
Low working capacity	1		12	46	34	41
Enlarged heart volume	0		5	19	17	19

suspected and cases with manifest cardiac involvement 5 years earlier. For the two groups in which myocardial lesions had been diagnosed or suspected 5 years earlier the follow-up findings were much the same as before except in regard to the incidence of abnormal ECGs on the orthostatic tests. The group of patients with presumptive myocarditis had the same incidence (approximately 10 per cent) of abnormal orthostatic ECG as did the control group (orthostatic reactions alone were not here regarded as manifestations of cardiac involvement).

For the group of dubious cases the incidence of abnormal resting ECGs was somewhat lower but the findings were in other respects consistent with those for the group with presumptive myocarditis.

The control group on the other hand showed significantly lower incidences of all abnormal findings with the exception of elevated antistreptolysin titer and sedimentation rates. Other abnormal findings were rare.

Comparison of present and previous findings in cases of presumptive myocarditis. The incidence of subjective symptoms at follow-up was found to be approximately 25 per cent as compared to 75 per cent for the same series during convalescence 5 years earlier. In the earlier investigation

40 per cent of the patients with normalization of the resting ECGs had shown abnormalities on the exercise ECGs during convalescence. At follow-up the exercise ECGs revealed abnormalities in 30 per cent of the patients but almost 20 per cent had already shown abnormalities on the resting ECGs. The working capacity during convalescence had been abnormally low in some 60 per cent of the small series; the figure for this series 5 years later was approximately 40 per cent. Enlarged heart volumes had been recorded in 3 of 23 patients (13 per cent) as compared to 20 of 85 patients in the follow-up study.

Discussion

There are no established clinical criteria in the diagnosis of myocarditis. A tentative diagnosis of this condition is quite common and for the analysis of a series of cases of myocarditis it is generally advisable to study a group of dubious cases alone, with a group in which the clinical diagnosis is reasonably certain. The present investigation demonstrates that two such groups may even after 5 years show a high degree of similarity.

The dubious group however had a significantly higher incidence of abnormal ECGs on orthostatic tests. Furthermore, the incidence of low working capacity and

enlarged heart volume was at least as high in this group as in the group of cases of presumptive myocarditis. This finding may suggest that the dubious group included a number of patients with vaso regulatory athenia—a state of deficient peripheral circulatory adjustment which besets the differential diagnosis between vasoregulatory athenia and acute myocarditis.^{11, 12, 13} Differentiation is not possible except by direct determination of stroke volume during exercise as in heart catheterization.

The third group which constituted the controls in this investigation had already been used for control purposes in studies of other series of patients in whom myocarditis was suspected.⁶ During the preceding 5 years however signs and symptoms not observed in the previous studies had emerged without any diagnosis of acute myocarditis and without any serious infectious disease of which the patients were aware. This group nevertheless was found to include a few patients with abnormal exercise ECGs and low working capacities; indeed at least one patient showed both electrocardiographic and other signs of acute myocardial lesions of the type here considered to be suggestive of acute myocarditis. The abnormalities observed in the two groups probably represent in corresponding degree myocardial damage which had developed during the preceding 5 years. The control series is too small however to permit any conclusion as to the incidence of myocarditis in an average population.

As was to be expected the distribution shows that diseases of streptococcal etiology predominated constituting roughly one half of the total series.—The incidence of acute myocardial lesions is known to be almost as high in cases of poliomyelitis.¹⁴ The series contains also a substantial number of cases of aseptic meningitis in circumstances which is consistent with several observations made in recent years.¹⁵ In point of fact both rheumatic fever and toxic scarlet fever have become more infrequent whereas aseptic meningitis has become increasingly common during recent years. Among the various forms of aseptic meningitis Russian spring and summer encephalitis has received particu-

lar attention not least by virtue of its capacity to produce endarteritis in which respect the disease is of peculiar interest from the prognostic and functional standpoint.¹⁶—The facilities available at that time did not permit examination of the present cases by virologic methods.

In the main group of 90 cases abnormalities were most frequently observed in the exercise ECGs and less frequently in the resting ECGs alone or in both resting and exercise ECGs. The investigation thus confirms as did the previous one⁶ the value of exercise electrocardiography in myocarditis—a finding reported by several authors.^{17, 18, 19, 20, 21, 22, 23} In the present series abnormal features were manifest in the resting ECGs alone in only 2 cases but in the exercise ECGs alone in 8 cases. In the first two instances the abnormalities consisted of atrioventricular block in cases of rheumatic fever; atrioventricular block is often difficult to evaluate on exercise electrocardiograms.

In electrocardiographic studies of cases of myocarditis abnormalities of the terminal segment have invariably been the most common. During convalescence however even disturbances in rhythm have not infrequently been recorded.^{24, 25, 26} Although the same was true of the present investigation it applied remarkably enough chiefly to cases of nonstreptococcal infectious diseases. In a few cases of poliomyelitis disturbances in rhythm were also noted on orthostatic tests. The majority of abnormalities were found in the aseptic meningitis group which also had an incidence of reduced working capacity and enlarged heart volume at least as great as that in the rheumatic fever group. These findings conflict with the earlier assumption that virus myocarditis invariably has a good prognosis *quoad restitutionem et quoad functionem* but they may be consonant with observations made by Weinstein in cases of poliomyelitis.²⁷

Under normal conditions there is a linear correlation between working capacity and stroke volume. Similarly the stroke volume is linearly correlated with the heart volume.²⁸ Under certain standardized conditions the intensity of exercise at a given heart rate is an indirect criterion of the stroke volume. Hence the working

capacity may be correlated with the heart volume both at rest and during exercise (for further references see Sjostrand^{4, 21}). It may a priori be assumed that in the presence of myocardial lesions the working capacity will be reduced because of impaired myocardial contractility and a consequently reduced stroke volume. Moreover in some cases circulatory insufficiency may result in an increase in the heart volume. The corollary is that if in cases in which there is a certain degree of myocardial damage associated with reduced stroke volume and increased heart volume the working capacity is related either to an irrelevant factor such as the body weight or to a factor influenced by the disease such as the heart volume the latter correlation will be most likely to reveal a significant deviation from normal. The foregoing conclusion is supported by the results of this investigation since correlation with the heart volume not only gave a distinctly higher incidence of abnormally low working capacity than did correlation with body weight but also showed in the individual cases more significant deviations from normal.

Approximately one patient in five was found to have an enlarged heart volume and this incidence did not differ appreci-

ably from group to group. It should be emphasized that a heart volume determined in the erect position without accurate evaluation of the contours of the heart will not as a rule show abnormal enlargement in cases of myocarditis since the increased volume generally fills within the wide range of variation reported for current methods and the influence of orthostatic factors on the volume is not taken into account.⁸

Comparison of the investigative results shows that enlarged heart volume and low working capacity were the two most frequently correlated findings followed by low working capacity and abnormal ECGs. Although these three factors—abnormal ECG, low working capacity and enlarged heart volume—were closely interrelated each of the first two factors was clearly correlated with the incidence of subjective symptoms and the first one was frequently concomitant with suspect phonocardiographic findings as well. The most conspicuous correlation was that between enlarged heart volume and working capacity; the weakest correlations were those between heart volume and respectively high antistreptolysin titers and suspect phonocardiographic findings (Table IX).

Subjective symptoms were correlated

Table IX. Incidence of abnormal and normal electrocardiograms, working capacities and heart volumes in relation to subjective symptoms, elevated antistreptolysin titers and/or sedimentation rates and suspect phonocardiograms.

	Number of cases	Electrocardiogram			Working capacity			Heart volume		
		Ab normal	Normal	Percent abnormal	Ab normal	Normal	Percent abnormal	Ab normal	Normal	Percent abnormal
Subjective symptoms	22	14	8	64	14	7	67	5	17	23
Elevated antistreptolysin titer and/or FSR†	25	15	10	43	14	11	56	5	20	20
Suspect ICG findings‡	21	15	6	70	10	11	48	4	17	19
Abnormal ECG§	41				21	15	58	10	26	26
Low working capacity	34	20	14	59				13	21	38
Enlarged heart volume	17	9	8	53	13	4	76			

FSR: 20 mm per hour (10 mm per hour) and above are considered abnormal.

†AST ≥ 400 units per milliliter, FSR ≥ 20 mm per hour.

‡Distal 1 sec. wave of high frequency and grossly 1 and in distal extremities.

§ECG cases with low working capacity and heart volume were 14 and 10.

¶Low working capacity was not determined in 1 case.

with abnormal electrocardiographic findings and with low working capacity to about the same degree. This observation is of practical clinical interest and corroborates the results of a previous investigation.¹

Recently Levander Lindgren examined 252 cases of myocarditis of different etiologies 6 months after the patients had been discharged from the hospital. The results of the ECG examinations are rather similar to the results obtained in this series: the frequency of persistent ECG changes at follow up was 20 per cent (mean) on examination at rest among various infectious diseases and rheumatic fever between 4.8 and 14.9 per cent and arrhythmia persisted in 45 per cent when the ECG at work was included. However most of the patients were symptom free or had symptoms indicating neurocirculatory asthenia. X-ray of the heart and physical working capacity was mostly normal.¹⁰

In the present study comparison of the follow up results with those recorded by the same methods during hospitalization and convalescence of the patients 5 years earlier revealed a substantial decrease in the incidence of subjective symptoms. The incidence of low working capacity had not declined to the same degree, however, and that of enlarged heart volume may well have risen, although the latter comparison was not conclusive because of inequality in the number of cases compared. In short, the fact emerges that after presumptive myocarditis due to infectious disease the subjective symptoms gradually subside, whereas electrocardiographic abnormalities, reduced working capacity and enlarged heart volume may persist to a remarkably high degree.

However, we do not state that the clinical significance of our findings is of great importance. The number of patients in our study was selected from an infectious diseases hospital material comprising approximately 15 000 patients and 5 years after discharge we found signs of persistent myocardial involvement in almost 30 to 40 cases yearly, in only half of those might the involvement be suspected on routine examinations and rather few have any symptoms at all. Most often the signs

will appear as *nœvi pigmentosi* (Levander Lindgren) of the electrocardiogram. Nevertheless the sequelae of acute postinfectious myocarditis should not be overlooked for sometimes and we suppose more often than is suspected they are the adequate explanations for an arrhythmia, a slight enlargement of the heart or an impaired physical condition. The differential diagnosis, particularly in instances of vasoregulatory asthenia, vegetative disturbances, nervous and cardiosclerosis is often extremely difficult. However in making the diagnosis the methods of exercise electrocardiography, physical working capacity test and a sensible determination of heart size are very useful and are to be utilized.

Summary

Ninety consecutive cases of acute infectious disease attended by signs highly suggestive of myocarditis (presumptive myocarditis group) were followed up after 5 years with examinations by the methods previously employed, namely electrocardiography at rest during exercise and on orthostatic tests, heart roentgenography and functional tests for determination of the physical working capacity. Identical examinations were carried out in 26 similar cases in which 5 years previously there had been signs possibly suggestive of myocarditis (dubious myocarditis group). Finally the investigation included 34 cases of acute infectious disease in which at the onset 5 years earlier there had been no signs of cardiac involvement (controls).

Approximately 25 per cent of the 90 patients in the first group reported subjective symptoms—fatigue, dyspœa, impaired physical condition, precordial pain—as compared to 75 per cent during prior convalescence. The corresponding incidence in the control group was about 10 per cent.

At follow up about 25 per cent were found to have elevated antistreptolysin titers and/or erythrocyte sedimentation rates, the incidence being the same in the control group.

Suspect phonocardiographic findings were recorded in 23 per cent (as against 3 per cent in the controls) but in no case were presystolic or diastolic murmurs noted.

The resting ECGs were abnormal in 19 per cent, the exercise ECGs in 30 per cent and the orthostatic ECGs in 10 per cent (0.6 and 12 per cent respectively for the controls). Sixty per cent of all abnormal ECGs were recorded either during or after exercise.

The majority of electrocardiographic abnormalities were referable to cases of aseptic meningitis, rheumatic fever and scarlet fever. In most cases the abnormalities involved the terminal complex. In addition to these abnormalities some cases of rheumatic fever exhibited atrioventricular conduction block, and others disturbances in rhythm.

The working capacity was abnormally low in 41 per cent of all cases of presumptive myocarditis (and in 3 per cent of the controls) irrespective of the nature of the initial infectious disease.

The heart volume was enlarged in 20 per cent, possibly with a somewhat higher incidence for patients with aseptic meningitis and rheumatic fever than for those with other infectious diseases. No case of enlargement of the heart was found in the control group.

Abnormal findings were frequently interrelated; in particular there was a high incidence of enlarged heart volume coincident with a low working capacity.

The incidences of abnormal findings were much the same in the dubious myocarditis group except for the orthostatic ECGs which showed abnormalities in 27 per cent in comparison with about 10 per cent in the other two groups.

Abnormal findings were recorded in a few cases in the control series. Only in one or two patients were there signs that myocardial lesions had developed during the past 5 years.

To sum up the overall results of this 5 year follow up study of 90 cases suggestive of postinfectious myocarditis (and compared with relevant control series) indicate that about 20 per cent of the patients still had subjective symptoms, some 15 to 20 per cent had abnormal ECGs, about 30 per cent had abnormal exercise ECGs, approximately 40 per cent had low working capacities and 15 to 20 per cent had enlarged heart volumes.

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Experimental and laboratory reports

Effect of a new hypotensive drug, ST155, on the systemic circulation

Winifred G. Nayler D.Sc.*

M. Rosenbaum MD MRACP

J. McInnes FRCS FRACS

T. E. Lowe D.Sc. MD FRCP FRACP

Victoria Australia

ST155 (2,2,6-dichlorophenyl 1-amino)imidazole HCl) is a recently developed antihypertensive drug which is shown in Fig. 1 structurally resembles tolazoline. Although preliminary clinical trials indicate that it is an effective hypotensive agent little is known about its mode of action. This paper describes a series of experiments planned to investigate the effect of ST155 on the systemic circulation of the dog.

Materials and methods

Dogs on heart lung bypass and dog isolated gracilis muscle preparations were used to investigate the effect of ST155 on the systemic circulation.

Anaesthesia. Dogs were premedicated with 30 mg. of morphine sulfate intramuscularly approximately 1 hour before anaesthesia was induced with sodium thiopentone (20 to 30 mg. per kilogram intravenously). A surgical level of anaesthesia was maintained with a nitrous oxide-oxygen mixture (2:1) delivered from an intermittent positive pressure respirator at a rate of 2 liters per minute with supplementary doses of thiopentone given from time to time as required.

Dog heart lung bypass preparation. The method used has been described previously.¹ Anaesthetized healthy mongrel dogs (12 to 15 kilograms) were heparinized (2 mg. per kilogram per hour intravenously) and placed on heart lung bypass using a Kay Cross disc oxygenator. The vascular system was perfused by means of a non-pulsatile (Momo) pump through the right common carotid artery at a constant flow rate which varied between 100 and 120 ml. per kilogram per minute in different experiments.

Appropriate cannulation allowed the independent measurement of venous outflow from the splanchnic, renal, lower inferior caval (IVC), superior vena caval (SVC) and azygos vascular fields and coronary sinus outflow. The mean systemic (arterial) pressure was indicated by a mercury manometer connected to a cannula inserted into either the left internal mammary or right femoral artery.

Isolated gracilis muscle preparation. This preparation has been fully described previously^{2,3} and consists of an isolated gracilis muscle perfused under conditions of constant flow with heparinized (2 mg. per kilogram) blood warmed to 37°C.

* From the Baker Medical Research Institute, Victoria, Australia.

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Address: Baker Medical Research Institute, Commercial Road, South Melbourne, Victoria, Australia.

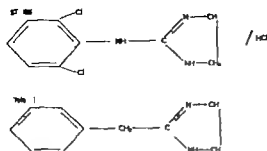


Fig. 1 Structure of tolazoline and ST155

that changes in resistance to blood flow through the muscle are reflected as changes in perfusion pressure. These changes were detected with a P23D(b) Statam strain gauge and displayed on an ultraviolet light photographic recorder.*

Drugs: The following drugs were used: 2-(2,6-dichlorophenyl)-5-methyl-1,3,4-oxadiazole HCl (as ST155†); sodium thiopentone (as Pentothal‡); epinephrine (as epinephrine tartrate§); norepinephrine (as Levophed bitartrate¶); pentolinum tartrate (as Anolymen‡); phenylephrine (as Dibenyl me¶); propranolol (as Inderal‡).

Dilutions of the various drugs were prepared in 0.9 per cent NaCl solution immediately before use. Drug concentrations are expressed in terms of the salt.

Results

Effect of ST155 on the dog heart lung bypass preparation. In 12 experiments the administration of 5 µg/Kg of ST155 to the perfusion system of dogs on heart lung bypass was followed by an immediate transient rise and then a sustained fall in systemic perfusion pressure. The results of a typical experiment shown in Fig. 2 indicate that the phase of reduced perfusion pressure persisted for approximately 30 minutes after which it gradually returned to the initial level. Doses of ST155 in excess of 5 µg/Kg caused a greater and more sustained decline in perfusion pressure. The administration of a second dose

of ST155 after all discernible effects of a first dose had disappeared was followed by a response which was identical with that recorded initially, that is by an initial transient rise followed by a sustained fall in perfusion pressure.

These biphasic changes in perfusion pressure were associated with a redistribution of blood throughout the various venous vascular fields. During the initial transient phase of increased perfusion pressure SVC, IVC and azygos blood flow decreased in all 12 experiments indicating probable vasoconstriction in these regional fields during this particular period of drug action. Some of these changes are shown in Fig. 3. Coronary blood flow increased during the phase of increased perfusion pressure as is shown in Fig. 3. Splanchnic and renal flows remained relatively constant in all experiments.

The initial pressor response caused by 5 µg/Kg of ST155 was not blocked by the prior administration of 15 mg/Kg of phenylephrine, a dose which is sufficient to abolish the pressor effect of 30 µg/Kg of epinephrine or norepinephrine.

The phase of reduced perfusion pressure which followed the initial transient rise was associated with further changes in the regional distribution of blood. In all 12 experiments blood flow through the IVC and azygos fields increased during the period of reduced perfusion pressure; in 9 experiments the splanchnic blood flow increased. Variable effects were found in the renal and SVC beds. These results relating only to blood flow during the period of reduced perfusion pressure are summarized in Table I in which the arithmetic mean and the range of the ratios of blood flow and perfusion pressure before and after the administration of ST155 are listed. In this table (Table I) the initial transient increase in perfusion pressure and the transient changes in regional blood flow associated with that initial increase have been omitted for the purposes of clarity. During the phase of reduced perfusion pressure the coronary minus blood flow showed a decline relative to that recorded during the period of increased perfusion pressure. The data in

*T. W. 3124 C. and Co. Ltd. Effect only and C. present on (London, pp. 1). British Drug Ltd. A. 1011.
 †D. 1011 & B. 1011 Ltd. A. 1011.
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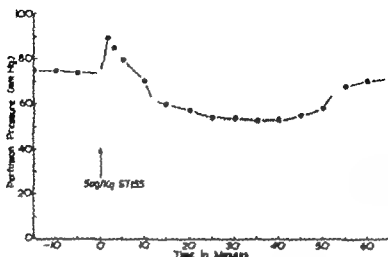


Fig. 2 Effect of ST155 on perfusion pressure in dog on heart lung bypass. Five micrograms per kilogram of ST155 was added at arrow, as indicated. Preparation perfused under condition of constant flow throughout the experiment.

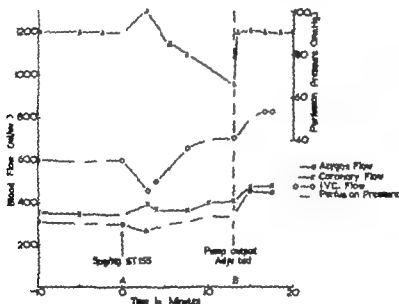


Fig. 3 Effect of ST155 on perfusion pressure and regional blood flow in dog on heart lung bypass. Under conditions of constant flow 5 $\mu\text{g/kg}$ of ST155 was added at arrow A as indicated. At B after the hypotensive action of ST155 was established the volume output of the pump was readjusted to restore perfusion pressure to the original level and blood flow in the various vascular fields perfused at the control pressure and in the presence of ST155 was redetermined.

in Table II indicate however that in 11 of 12 experiments coronary sinus blood flow recorded during the period of ST155 reduced perfusion pressure was equal to or greater than that recorded during the initial control period before the administration of ST155.

In 5 experiments approximately 15

minutes after 5 $\mu\text{g/kg}$ of ST155 had been administered to the preparation the volume output of the pump was adjusted to counterbalance the hypotensive action of ST155 and the perfusion pressure maintained at the initial control level. Under these conditions the action of ST155 was associated with marked increases in blood

Table I Effect of 5 µg/kg of ST155 on perfusion pressure and regional blood flow in dogs on heart lung bypass

Experiment No.	Fractional change $\left(\frac{F}{I}\right)$						
	Perfusion pressure	Coronary flow	I.V.C. flow	Axillary flow	SVC flow	Splanchnic flow	Renal flow
12							
Mean	0.71	1.1	1.3	1.7	1.0	0.97	0.88
Range	0.6-0.8	0.7-1.5	1.1-2.2	1.0-1.3	0.8-1.3	0.6-1.3	0.6-1.1

Mean values obtained were expressed as ratio $\frac{F}{I}$ where F = flow, perfusion pressure recorded during the hypotensive phase after the administration of 5 µg/kg of ST155 and I = control flow, perfusion pressure recorded immediately before the administration of ST155. Total body flow measured continuously throughout the experiment.

Mean values obtained were expressed as ratio $\frac{F}{I}$ where F = flow, perfusion pressure recorded during the hypotensive phase after the administration of 5 µg/kg of ST155 and I = control flow, perfusion pressure recorded immediately before the administration of ST155. Total body flow measured continuously throughout the experiment.

Table II Effect of 5 µg/kg of ST155 on perfusion pressure and coronary sinus blood flow in dogs on heart lung bypass

Experiment No.	Perfusion pressure (mm Hg)		Coronary sinus blood flow (ml/min)	
	Before ST155	After ST155	Before ST155	After ST155
1	83	65	785	287
2	73	55	470	441
3	90	60	165	206
4	120	80	149	193
5	95	80	236	285
6	95	70	196	170
7	90	70	236	363
8	95	70	272	280
9	100	80	175	200
10	90	60	171	194
11	90	65	337	390
12	90	60	187	197

Perfusion pressure and coronary sinus blood flow were determined by Co. perfusion catheters inserted into the coronary sinus and the descending aorta.

flow in the I.V.C., SVC, axillary and coronary vascular fields. The results from a typical experiment are displayed in Fig. 3 the other 4 experiments yielded similar results.

In 5 experiments after the hypotensive action of ST155 had been established in a particular heart lung bypass preparation 10 mg/kg of pentolinium tartrate was administered followed 15 or 20 minutes later by the further administration

of 5 µg/kg of ST155. The typical results of such an experiment are displayed in Fig. 4 and indicate that the hypotensive action in dogs is blocked by the prior administration of pentolinium tartrate. The initial pressor response however remained.

In 6 other experiments the effect of 5 µg/kg of angiotensin on dogs on heart lung bypass was established before the administration of 5 µg/kg of ST155.

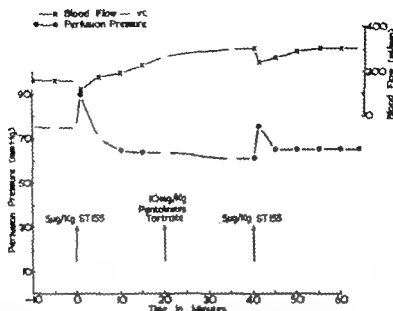


Fig. 4. Effect of pentolinum tartrate on response of dog on heart lung bypass to ST155. Five micrograms per kilogram of ST155 was added to the perfusate as indicated before and after the addition of 10 mg/kg of pentolinum tartrate to dogs on heart lung bypass perfused under conditions of constant flow.

argon during the hypotensive phase which followed the introduction of ST155. The results of these experiments are summarized in Table III and indicate that the effect of angiotensin on perfusion pressure and regional blood flow was only slightly diminished by the presence of ST155.

ST155 was administered to 3 other preparations 15 minutes after the prior administration of 30 mg/kg of propranolol, a dose which is sufficient to abolish the hypotensive effect of 100 µg/kg of ST155. Under these conditions 5 to 10 µg/kg of ST155 failed to produce any hypotensive effect; the initial pressor response was still evident.

Effect of ST155 on the isolated gracilis muscle preparation. The addition of ST155 at 37°C to the perfusion system of isolated gracilis muscle preparations failed to cause a change in the perfusion pressure which was significantly greater than that caused by the control injection of saline. The data listed in Table IV show that the addition of a wide range of doses of ST155 failed to exert any direct effect on the perfusion pressure in this isolated system.

Discussion

These findings indicate that the administration of ST155 to dogs which are

on heart lung bypass and in which the baroreceptor system has been left intact results in an immediate transient increase followed by a sustained fall in perfusion pressure. These changes were found to be associated with changes in regional blood flow. During the conditions of constant flow used in these experiments both perfusion pressure and total flow through individual vascular beds vary so that only overall trends in the resistance to blood flow through individual vascular fields can be ascertained.

Immediately after the administration of ST155 the perfusion pressure increased, reflecting an overall increase in total peripheral resistance which was not abolished by a diuretic blockade. During this transient phase of increased perfusion pressure skeletal muscle blood flow represented by the azygos, lower IVC and part of the SVC flow decreased indicating vasoconstriction. Some of these changes were shown by the data displayed in Fig. 3. Coronary flow increased during this initial phase of increased perfusion pressure indicating either a lesser degree of vasoconstriction relative to that in other vascular fields or vasodilation. During the phase of reduced perfusion pressure muscle and coronary blood flow

Table III Effect of 5 µg/kg of angiotensin on systemic perfusion pressure and coronary and inferior vena caval blood flow in the presence and absence of 5 µg/kg of ST155

Experiment No	Angiotensin (5 µg/kg)	Before ST155			After ST155		
		Perfusion pressure (mm Hg)	Coronary flow (ml/min)	I.V.C. flow (ml/min)	Perfusion pressure (mm Hg)	Coronary flow (ml/min)	I.V.C. flow (ml/min)
14	Before	110	492	413	95	555	577
	After	170	617	315	135	675	478
15	Before	75	353	355	45	331	572
	After	115	571	741	85	361	371
16	Before	100	231	315	75	319	413
	After	180	536	250	150	444	230
17	Before	95	239	462	60	353	557
	After	150	364	215	90	438	340
18	Before	85	187	462	7	222	600
	After	170	275	211	160	300	316
19	Before	110	714	251	80	300	275
	After	230	600	165	190	465	193

Table IV Effect of ST155 on the perfusion pressure in the dog isolated gracilis muscle preparation

Experiment No	Perfusion pressure (mm Hg)					
	Control	After saline	After saline + ST155 (µg)			
			10	0.1	0.001	0.0001
1	175	110	110	110		110
2	100	95		95	95	
3	110	100		100		100
4	95	90	90	90	90	90

increased indicating vasodilation. Renal and splanchnic flows showed variable changes indicating either a lesser degree of vasodilation relative to that in the coronary and muscle beds or even vasoconstriction.

In those experiments in which the volume output of the pump was increased in order to compensate for the ST155 induced fall in perfusion pressure, muscle and coronary blood flow showed a marked

increase when compared with that recorded at the same perfusion pressure prior to the addition of the drug. Splanchnic and renal blood flows remained approximately at the control level indicating that ST155 had had little effect on the resistance to blood flow through these particular vascular fields.

Although ST155 had a marked effect on skeletal muscle blood flow in the intact dog on heart lung bypass, a direct and

on blood flow through the isolated gracilis muscle preparation was not detected. These results may be interpreted to mean that ST155 acts centrally via the nervous system and this interpretation is supported by the complete blocking action of Ansohysen. Since β adrenergic blockade abolished the hypotensive action of ST155 it seems to be probable that the β adrenergic receptors may be involved in the hypotensive action of this drug.

Summary

Dogs on heart lung bypass and perfused gracilis muscle preparations were used to investigate the effect of the recently introduced hypotensive drug ST155 on the systemic circulation.

Five micrograms per kilogram of ST155 caused a transient rise followed by a sustained fall in the perfusion pressure of dogs on heart lung bypass. Changes in the regional distribution of blood were associated with these changes in perfusion pressure the hypotensive response being associated with a marked increase in muscle blood flow.

Phenoxybenzamine failed to abolish the initial pressor action of ST155, propranolol and Ansohysen abolished its hypotensive action.

ST155 failed to affect the perfusion pressure in isolated gracilis muscle preparations perfused under conditions of constant flow.

We gratefully acknowledge the gift of ST155 from Boehringer Ingelheim Pty Ltd and of Isodril from Imperial Chemical Industries. Phenoxybenzamine was kindly supplied by Smith Kline and French Pty Ltd.

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Changes in capillary filtration coefficient in the forearm during emotional and postexercise hyperemia and after intra-arterial adrenaline, acetylcholine, and isopropylnoradrenaline

Jan Brod M.D. D.Sc.

Ivo Prerovsky M.D. C.Sc.

Vilas Ulich M.D. C.Sc.

Jiri Linkart M.D. C.Sc.

Horst Heins M.D. ¹

Prague Czechoslovakia

It has been repeatedly demonstrated that during the emotional reaction to stressful mental arithmetic blood flow increases markedly in the forearm and calf muscles^{1,2} Barcroft³ and Blair⁴ and associates have produced evidence that this emotional vasodilation is at least partly mediated through sympathetic cholinergic fibers which are also thought to mediate the vasodilator response when a well defined hypothalamic area in cats is stimulated.⁵ The emotional vasodilation is only part of a generalized hemodynamic response consisting of vasoconstriction in the kidneys, placental area and lung and of an increase in cardiac output with a shift of blood to muscle.⁶ In this respect the reaction resembles the hemodynamic changes with muscular exercise. Brod, Flej⁷ and Ulich⁸ have further demonstrated that whereas during muscular exercise blood flow increases in response to an increase in the metabolic demands of the muscle, muscular hyperemia during

emotion is not proportionate to any change in muscle metabolism and is independent of any change in the consumption of oxygen and glucose. There is also some evidence based on the clearance rate of radioactive iodine (¹²⁵I) from muscle that the extra blood during emotional hyperemia in muscle flows through channels other than those used during a comparable increase in blood flow produced by muscular exercise.

The question of a dual vascular pathway in muscle is open to discussion. Its presence is claimed by some,⁹ but denied by most of the anatomists. The method of ¹³¹I clearance is also open to criticism in view of a relatively slow diffusibility of this substance which may be a limiting factor during a marked increase in blood flow.¹⁰

It would seem to be important therefore to investigate by other techniques the possibility of different blood channels during muscular exercise and emotion. The size of the capillary surface area can be

¹ In the Institute of Cardiovascular Research, Prague, Czechoslovakia.

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Present address: Dr. Horst Heins, Director, Institute for Cardiovascular Research, 8090 Bad Nauheim, Germany.

Address: 24 Department of Medicine, Charité Hospital, Berlin, East Germany.

assessed by the measurement of the capillary filtration coefficient (CFC)^{12,13} provided that the permeability of the capillary wall does not change. This technique has also been used to investigate the influence of some of the substances thought to be important in mediating emotional hyperemia on capillary surface area.

Methods

The investigation was carried out on 23 volunteer subjects in a quiet laboratory in the morning hours after a light breakfast. Most of the subjects were suffering from various mild chronic conditions but had no evidence of impaired peripheral circulation in the upper extremities. The brachial artery and one of the veins in the left forearm were cannulated percutaneously by polyethylene catheters under local anesthesia using Holmgren's modification¹⁴ of the Seldinger technique.¹⁷ Blood flow was measured by the mercury-in-rubber plethysmograph¹⁸ placed in the middle of both forearms with the right forearm being used for control measurements.

The CFC was measured in both forearms using the increase in volume after an increase in pressure of 60 mm Hg in the occluding cuff on the arm. After the rapid initial change the increase in volume in the extremity between the third and fifth minutes after venous occlusion is approximately linear. This slope was used for measurement of the CFC. Venous pressure was registered simultaneously and was invariably stabilized at the time of measurement of the CFC. The effective capillary pressure available for filtration was assumed to be 80 per cent of the venous pressure according to Mellander.¹⁹ The CFC was expressed in milliliters per 100 ml per minute per 1 mm Hg.

Emotional stress was produced by having the subject subtract repeatedly a number from a preceding result at such a rate that he was unable to cope. The duration of this stimulus ranged from 10 to 15 minutes during which time arterial pressure, blood flow, and CFC were registered. The procedure has been described previously.⁷

In the first 9 experiments in which the effect of muscular exercise was investigated the subject lifted with his hand a weight of

3 kilograms at 2-second intervals for 2 to 3 minutes. In the other 14 investigations the subject was asked to open and close the fist rhythmically for 5 minutes at a rate that would produce a hyperemia comparable in degree to that produced by mental stress. Because of the technical difficulties in measuring the investigated parameters during actual exercise the measurements were performed as soon as possible after cessation of the exercise and assessments of blood flow were carried out before and after the estimation of CFC in order to ensure that the hyperemia persisted throughout the measurements. It is understood that this is not a steady state condition that is believed to be essential for the registration of the CFC. However, since accelerated blood flow was demonstrated both before and after the measurement of CFC, the registered CFC represents an integrated volume that was registered undoubtedly still before the postexercise hyperemia had subsided.

In another 14 subjects the influence of an infusion of acetylcholine, adrenaline, and isopropylnoradrenaline into the brachial artery of the experimental forearm was investigated. In order to exclude the possibility that the pharmacologic agents acted in some way other than only locally the data were compared to those obtained simultaneously in the control forearm of all 10 subjects treated with isopropylnoradrenaline in 5 of the 8 subjects treated with acetylcholine and in 7 of the 8 subjects treated with adrenaline. The intrarterial infusion was administered from a constant rate pump and the dosage was adjusted in each individual subject so as to produce an increase in forearm blood flow comparable in degree to that produced by the period of stressful mental arithmetic. It ranged from 0.011 to 1.156 g per minute for adrenaline, from 15.6 to 109.0 g per minute for acetylcholine, and from 0.031 to 0.107 g per minute for isopropylnoradrenaline. When several pharmacologic agents were tried in the same subject a sufficient interval was allowed between infusions to ensure a return of forearm blood flow to a resting state. The patients did not complain of any undue discomfort.

The results were evaluated statistically using Student's *t* test.²⁰

Results

Vascular exercise and mental arithmetic
In the first series of experiments we compared CFC during postexercise muscle hyperemia with that accompanying stressful mental arithmetic in 9 subjects and the data are summarized in the upper part of Table I. A typical result is demonstrated in Fig. 1. It may be seen that during postexercise hyperemia CFC was markedly elevated from about 0.006 to 0.044 ml/100 ml/min/1 mm Hg but remained virtually unchanged or tended to decrease slightly during the hyperemia accompanying mental stress. Although muscle blood flow registered immediately on cessation of exercise was higher than flow during emotional stress it decreased in the course of the postexercise period to levels comparable to those during mental arithmetic. However the CFC during that period was still markedly elevated.

An analogous behavior of CFC during the postexercise hyperemia was noted in all of the 9 subjects. The increase in forearm blood flow in the postexercise period just before CFC was registered ranged from +33 to +221 per cent with an average of +139 per cent ($p < 0.005$) whereas the increase in CFC ranged from +15 to +499 per cent with an average of +177 per cent ($p < 0.025$). On the other hand in the 8 experiments in which valid data on the CFC were obtained during emotional stress forearm blood flow at the period closest to the measurement of the CFC was increased by +23 to +314 per cent with an average of +140 per cent ($p < 0.005$) but the changes in the CFC were irregular and did not parallel changes in the forearm blood flow. They fluctuated between 50 and 161 per cent of the control value the average change being 95.2 per cent for the whole group. Although the average values for the increase in forearm blood flow were practically of the same magnitude during emotion after exercise

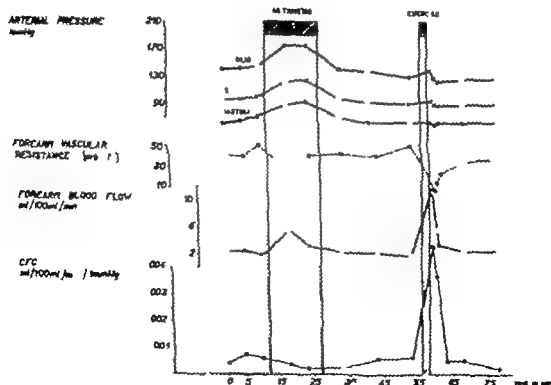


Fig. 1 Comparison of the hemodynamic change caused by emotion 1 trial (shaded area) and exercise in Subject M.B.

Table 1 Comparison of changes during stressful mental arithmetic and after exercise

Subject	Age Sex	Diagnosis	Intramedic				Extramedic			
			Mean arterial pressure (mm Hg)	Forearm blood flow (ml/100 ml/min)	Forearm vascular resistance (arbitrary units)	CPL (ml/100 ml/min Hg)	Mean arterial pressure (mm Hg)	Forearm blood flow (ml/min)	Forearm vascular resistance (arbitrary units)	CNC (ml/100 ml/min Hg)
1 Jh	58 M	1 chronic disease of lower extremities	b 96.1 A 114.0 c 119.0	1.4 3.1 27.1	68.7 37.6 55.0	0.0044 0.0030 68.0	b 107.0 E 95.0 c 88.0	1.5 4.8 320.0	71.4 19.8 27.8	0.0060 0.0174 290.0
2 Mv	20 M	Glomerular nephritis chronic	b 123.0 A 130.0 c 107.0	2.1 4.8 2.8	57.3 27.1 47.0	0.0028 0.0045 161.0	b 121.5 E 116.0 c 96.0	1.8 2.8 155.0	67.6 41.4 61.3	0.0033 0.0045 116.0
3 JH	51 M	1 chronic disease of lower extremities	b 95.7 A 108.0 c 113.0	1.3 5.2 400.0	76.0 21.0 28.0	0.0046 0.0023 50.0	b 97.0 E 90.0 c 92.8	1.4 2.4 171.0	67.8 37.5 55.4	0.0024 0.0068 74.0
4 VB	19 M	State after nephrectomy for congenital hydropnephrosis	b 97.0 A 122.4 c 128.0	2.3 5.7 218.0	42.2 21.5 51.0	0.0063 0.0036 57.0	b 91.6 E 90.0 c 96.0	2.2 5.8 263.0	43.8 15.5 35.0	0.0064 0.0371 599.0
5 AJ	62 M	Vascularoma	b 99.8 A 100.0 c 100.0	1.7 2.1 129.0	58.7 47.6 81.0	0.0037 0.0025 123.0	b 105.0 E 104.0 c 99.0	1.8 6.3 350.0	60.0 16.5 28.0	0.0051 0.0102 200.0
6 BJ	51 F	Renal artery stenosis hypertension	b 94.8 A 119.5 c 126.0	1.5 2.3 153.0	63.2 52.0 82.0	0.0072 0.0048 94.0	b 99.7 E 102.0 c 103.0	2.1 4.6 218.0	47.6 22.2 46.0	0.0070 0.0201 287.0
7 FT	37 M	Esophageal hypertension	b 102.0 A 116.0 c 104.0	2.2 9.1 414.0	47.4 12.8 27.0	0.0024 0.0023 96.0	b 115.0 E 110.0 c 96.0	2.8 4.6 164.0	41.1 24.0 59.0	0.0039 0.0045 115.0
8 JB	30 M	Mitral stenosis	b 75.5 A 79.0 c 105.0	1.3 2.8 219.0	56.7 8.0 40.0	0.0046 0.0052 113.0	b 81.0 E 76.0 c 94.0	1.5 2.0 135.0	54.0 38.0 0.0	0.0031 0.0052 168.0

the fact demonstrated in Fig. 1 was obvious also in all of the other experiments, namely that the first values after exercise were considerably higher than those observed throughout the entire period of the emotional stress. The similarity of the averages was due to the declining trend of the post-exercise blood flow during the period of observation.

In order to study the CFC at more comparable levels of blood flow at the beginning of the postexercise period and during mental arithmetic we carried out 6 additional experiments in which the exercise consisted of a mere opening and closing of the fist although this caused some difficulty because of the short duration of the postexercise hyperemia. These results are shown in the lower part of Table 1. In 3 of the experiments however the volume curves were technically inadequate and in another subject (J V)

the increase in flow after exercise was again much higher than during emotion. In the other 2 subjects (Z L, A L) in whom the requirement of comparability of the increases in postexercise and emotional flows was fulfilled CFC was elevated after exercise and actually showed a drop during emotional stress.

The values of CFC recorded in subjects during comparable increases in flow after muscular exercise and mental stress are summarized in Fig. 2. They illustrate the fact that both stimuli increase forearm blood flow although the CFC rises only after muscular exercise and not during muscular hyperemia produced by mental stress. The difference in the reaction of the CFC during mental stress and after exercise at comparable flow levels is significant ($p < 0.025$).

Pharmacologic agents. The influence of adrenaline and acetylcholine was tested

Table 11 Change during infusion of adrenaline

Subject	Age Sex	Diagnosis		Mean arterial pressure (mm Hg)
1 G R	35 M	Essential hypertension	b	12.0
			A	12.0
2 J T	42 M	Essential hypertension	b	128.0
			A	134.4
3 J I	41 M	Varicose veins	b	91.0
			A	92.0
4 F C	35 M	Essential hypertension	b	143.0
			A	143.0
5 J J	38 M	Varicose veins	b	96.0
			A	89.0
6 M I	26 F	Neurocirculatory asthenia	b	121.0
			A	120.0
7 S R	41 M	Essential hypertension	b	132.0
			A	126.5
8 J V	36 M	Chronic glomerular nephritis	b	134.0
			A	161.0

CFC = pulse frequency coefficient, in % per 100 mm Hg. b = before, A = after.
 77 percentages were calculated from the pre-exercise and post-exercise values.
 1 Adrenaline, 2 Acetylcholine, 3 Adrenaline, 4 Adrenaline, 5 Adrenaline, 6 Adrenaline, 7 Adrenaline, 8 Adrenaline.

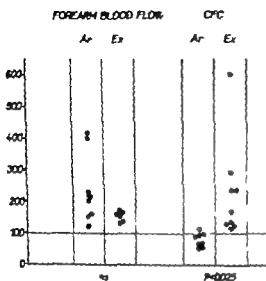


Fig 2 Changes in capillary filtration coefficient caused by emotion and exercise at a comparable increase in blood flow

in 8 subjects and the influence of isopropylnoradrenaline was studied in 10 subjects with overlapping Isopropylnoradrenaline was included after we realized how difficult it is to maintain the hyperemia produced by the intra arterial infusion of adrenaline. The data are summarized in Tables II, III and IV.

The results were expressed as a per cent of the value expected if blood flow in the experimental forearm would change in a fashion parallel to that in the control forearm.

ADRENALINE In 7 of 8 experiments adrenaline produced a rise in blood flow in the experimental forearm which ranged from 108 to 203 per cent of flow in the control forearm (Table II). The increased flow was due in all instances to a drop in the forearm vascular resistance. In 5 subjects the hyperemia persisted for more than 5 minutes. CFC fluctuated slightly on both sides of the resting values. In 7

Forearm blood flow (ml/100 ml/min)			Forearm vascular resistance (arbitrary units)			CFC (ml/100 ml/min/1 mm Hg)		
Exper	Control	%	Exper	Control	%	Exper forearm	Control forearm	%
1.5	—	—	81.6	—	—	—	—	—
2.1	—	—	60.7	—	—	—	—	—
3.4	3.2	—	37.6	39.7	—	0.0037	0.0031	—
3.9	3.0	116.3	34.5	42.3	86.2	0.0048	0.0074	39.6
3.8	2.0	—	23.7	43.6	—	0.0055	0.0081	—
6.2	1.7	190.0	14.9	34.2	5.9	0.0061	0.005	80.3
6.9	4.0	—	21.0	35.8	—	0.0060	0.005	—
13.0	5.7	203.0	11.2	38.1	50.5	0.0090	0.0057	118.8
4.7	4	—	20.3	22.9	—	0.0105	0.010	—
4.2	3.4	109.3	21.2	26.2	90.1	0.0068	0.0142	8.1
1.1	1	—	93.2	1.1	—	0.0037	0.0039	—
1.6	0	106.0	7.4	60.5	07.7	0.007	0.0047	60.6
9	1.9	—	44.8	69.5	—	0.009	0.0058	—
4.1	1.4	128.5	30.8	90.3	51.8	0.011	0.0066	10.3
2.9	3.3	—	54.0	49.4	—	0.0061	0.005	—
3.0	9	116.2	54.5	56.5	87.0	0.0045	0.0049	48.0

Table III Changes during infusion of acetylcholine

Subject	Age Sex	Diagnosis		Mean arterial pressure (mm Hg)
1 TR	35 M	Essential hypertension	b ACH	127.0 128.0
2 JT	42 M	Essential hypertension	b ACH	133.0 125.0
3 JL	44 M	Varicose veins	b ACH	90.0 93.5
4 FC	55 M	Essential hypertension	b ACH	144.0 141.5
5 JJ	38 M	Varicose veins	b ACH	90.0 86.5
6 MP	26 F	Neurocirculatory asthenia	b ACH	118.5 112.5
7 SR	41 M	Essential hypertension	b ACH	130.5 135.5
8 JV	26 M	Chronic glomerular nephritis	b ACH	155.0 160.0

CFC: Capillary flow time difference between experimental and control sides. ACH: Acetylcholine. b: before infusion. T: percent increase calculated from the pooled data. d: after 4.5 l. significance of the results calculated from the non-paired test.

of these subjects comparison with the control forearm showed that a decreasing tendency was present in 5, whereas CFC remained virtually unchanged in the other 2 (102.3 and 113.8 per cent).

ACETYLCHOLINE. Forearm blood flow was increased by acetylcholine in all 8 subjects and the forearm vascular resistance decreased in all of them (Table III). CFC increased by more than 0.0010 ml/100 ml/min/1 mm Hg in 1 subject (JT), remained practically without change in 5 (TR, JL, FC, MP, JV) and decreased in 1 (JJ) whereas the change could not be assessed with precision in the one other subject. Comparable data with the other forearm were obtained in 4 subjects. CFC showed an increasing trend (above 20 per cent) in 1 and did not exceed this arbitrary limit in the other 3 subjects.

ISOPROPYLNORADRENALINE. This drug produced a rise in the forearm blood flow

of 107.5 to 397.0 per cent of the expected values in 9 of 10 subjects with a constant drop in the forearm flow resistance (Table IV). In the other subject (JV, No. 10) the resting blood flow recorded prior to infusion was still elevated after the preceding exercise despite a lapse of more than 30 minutes. It is probably for this reason that no increase in flow could be demonstrated during the infusion of isopropylnoradrenaline. CFC in this subject dropped to 78.9 per cent of the expected value. In one subject the CFC increased by more than 20 per cent as compared with the other side (JV, No. 5). In 4 subjects the changes in CFC did not exceed the limit and in 3 the response of CFC was actually less on the experimental than on the control side (MP, No. 3, SR, No. 4 and ZL, No. 6) amounting only to from 30.7 to 67.3 per cent of the values on the control forearm. In one sub-

Forearm blood flow (ml/100 ml/min)			Forearm vascular resistance (arbitrary units)			CFC (ml/100 ml/min/1 mm Hg)		
Exper	Control	σ	Exper	Control	σ	Exper forearm	Control forearm	σ
1.9	—	—	66.8	—	—	0.0019	—	—
2.8	—	—	45.7	—	—	0.0019	—	—
3.3	—	—	40.3	—	—	0.0078	—	—
9.2	—	—	13.6	—	—	0.0042	—	—
4.0	1.7	—	22.5	53.0	—	0.0077	0.0091	—
4.7	1.8	115.5	19.9	53.5	87.7	0.0086	0.0042	242.0
5.1	2.6	—	28.0	55.4	—	0.009	0.0069	—
17.3	3.3	270.1	8.1	42.5	37.6	0.0072	0.0065	92.7
3.3	2.9	—	27.3	31.1	—	0.006	0.0129	—
14.2	—	—	6.1	—	—	0.0030	—	—
1.2	1.7	—	103.1	72.3	—	0.0078	0.0064	—
2.1	1.6	187.0	53.6	70.5	57.6	0.0027	0.0056	108.2
2.8	1.7	—	46.6	75.5	—	0.0090	0.0058	—
7.9	1.5	370.0	17.2	11.3	29.8	—	—	—
2.9	2.7	—	53.5	57.5	—	0.0037	0.0037	—
13.9	2.5	490.0	12.4	64.0	20.4	0.0030	0.0030	100.0

Figure 15.14

ject (A.L. No. 9) the CFC could not be assessed with precision.

Discussion

The method for measuring CFC is rather crude so that only large changes can be accepted as being meaningful. It was important to keep this in mind in the experiments with mental stress which affect, of course, both extremities and where it was necessary therefore to use the same extremity as a control. We have also proceeded in the same way in the analysis of the experiments with muscular exercise because these were done in the same subjects and during the same experimental session as the investigations with mental stress. We thought that it would be more advantageous to analyze both sets of data in the same way, the crucial point being the comparison of the behavior of the capillary bed during muscular

stress with that during muscular exercise.

In the experiments with intra-arterial infusion of the various pharmacologic agents we relied on the comparison of the changes in the experimental extremity with those in the control side in order to exclude a possible action of the drug which penetrated beyond the capillary bed of the experimental extremity and also to exclude spontaneous variations.

The CFC can be considered to be an indicator of the number of patent capillaries.¹¹ The increase in the number of capillaries that are open during muscular exercise has been well established since the time of Krogh.¹² The marked and uniform increase in the CFC during the period after muscular exercise corroborates the validity of Folkow's assumption concerning interpretation of the CFC and is in keeping with changes in the CFC

Table IV Changes during infusion of isopropylnoradrenaline

Subject	Age Sex	Diagnosis		Mean arterial pressure (mm Hg)
1 I C	35 M	Essential hypertension	b I	140.5 149.0
2 J J	38 M	Varicose veins	b I	85.0 76.0
3 M I	76 J	Neurocirculatory asthenia	b I	117.5 112.5
4 S R	31 M	Essential hypertension	b I	132.0 131.0
5 J A	26 M	Chronic glomerular nephritis	b I	167.5 155.0
6 Z I	30 M	Chronic pyelonephritis	b I	111.0 109.0
7 Z R	28 M	Chronic glomerular nephritis	b I	124.0 126.0
8 O A	49 M	Varicose veins	b I	113.0 117.6
9 A I	28 M	Buerger's disease	b I	95.0 97.0
10 J A	46 M	Nephrothrosis	b I	100.0 101.5

CFC Cap R (12) eff le 1 1 pr 1 prn total b B f 1 1 cap pr p 1 end end
TI per m % (ml) d f m t p cool de and way d f l 1 cap pr p 1 end end
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reasons it is impossible to estimate capillary filtration during the actual exercise. It is well known and has been also borne out by the data of our present work that immediately upon cessation of exercise muscle blood flow starts to drop. In most experiments it follows an exponential like curve. Although we have tried to start the measurements as soon as possible after exercise some time may be lost before the assessment of CFC can be begun. It is very likely however that during the actual exercise the flow was even higher and the same might have been true of the capillary filtration rate. Thus it may be objected that the measurement during the immediate postexercise period was not

carried out under steady state conditions. However our primary interest was not with the behavior of the muscle capillary bed during and after exercise this being well known—and our data are in keeping with the established facts. The changes in the CFC during the postexercise muscular hyperemia were used simply for comparison with the behavior of the muscle capillaries during muscular hyperemia produced by emotional stress. This did not change significantly the CFC although muscle blood flow exhibited an increasing trend in practically all experiments. It may be argued that the difference between muscular exercise and mental arithmetic is due to the previously mentioned fact that at

Forearm blood flow (ml/100 ml/min)			Forearm vascular resistance (arbitrary units)			CFC (ml/100 ml/min/1 mm Hg)		
Exper	Control	%	Exper	Control	%	Exper forearm	Control forearm	
6.0	3.2		23.4	43.2		0.0064	0.0060	
9.4	2.8	181.5	15.8	53.2	54.9	0.0084	0.0072	106.5
2.7	2.4		23.3	35.4		0.0075	0.0070	
5.8	3.5	107.5	13.1	21.7	97.3	0.0044	0.0059	118.9
1.5	2.6		78.3	46.1		0.0035	0.0051	
1.7	2.1	138.5	66.2	55.6	72.2	0.0037	0.0085	6.3
2.6	1.4		30.8	94.3		0.0100	0.0048	
4.1	1.7	191.5	32.0	109.0	52.2	0.0047	0.0044	30.7
3.4	3.2		49.7	52.5		0.0038	0.0057	
4.2	3.5	112.9	—	—	87.0	0.0074	0.0013	138.0
3.1	5.1		33.8	21.8		0.0078	0.0043	
1.9	4.5	181.5	22.0	24.2	55.3	0.0012	0.0079	63.6
3.0	2.8		24.6	44.3		0.0037	0.0077	
5.6	2.2	307.0	7.8	53.0	18.9	0.0031	0.0067	115.5
2.8	2.4		40.3	47.1		0.0059	0.0086	
9.0	3.1	250.0	13.1	37.9	39.8	0.0043	0.0060	104.5
4.4	3.4		21.6	27.9				
6.9	4.2	128.0	16.7	26.5	78.8			
6.2	6.3		14.4	15.4		0.0081	0.0056	
3.9	6.1	65.0	26.1	16.8	153.3	0.0050	0.0043	8.4

Fig. 1. The table

least immediately after muscular exercise muscle blood flow increased more than during emotional stress. However if the opening of the capillary bed is dependent only on physical factors such as critical opening pressure¹ there should be no difference between the number of open capillaries if blood flow reaches the same level during postexercise hyperemia as during emotional hyperemia. We have no reason to assume that the unchanged CFC during the emotional increase in blood flow would result from a decreased permeability of the capillary wall. Hence the unchanged or even diminished CFC when forearm blood flow increases suggests that this extra blood during emotional

hyperemia does not perforce an increased filtering surface. This is in agreement with our previous findings that show no change in the clearance rate of radioactive iodine (¹³¹I) from muscle during the emotional increase in blood flow in the forearm. Similarly there was no increase in the clearance rate of the intramuscularly injected venous 133 during emotional hyperemia at least in part of the experiments carried out by Lassen (unpublished data) and ourselves (unpublished data).

It has been shown that emotional vasodilation can be partly blocked by at least ganglion anesthesia and atropine.¹ This result suggested that vasodilatation is mediated by the cholinergic sympathetic

nervous fibers. These are also involved in the muscular vasodilatation produced by stimulation of a well defined hypothalamic area.⁴ It was thought that the remainder of the vasodilatation after atropinization might be produced by circulating adrenaline which is corroborated by recent evidence of a diminished degree of emotional vasodilatation after β -adrenergic receptor blockade by propranolol.⁵ Both acetylcholine and adrenaline are probably involved in the production of emotional vasodilatation. If so an infusion of any of these substances in doses producing vasodilatation similar to that caused by the stress should also remain without effect on the CFC. The results of our investigations are in full agreement with this assumption. The difficulty of maintaining vasodilatation after adrenaline for a sufficient length of time necessary for the measurement of the CFC has been already mentioned since this substance acts on both alpha and beta receptors. For that reason the effect of isopropylnoradrenaline (acting only on beta receptors) was also tested. Although this substance produced vasodilatation in 9 of 10 observations CFC increased in 1, decreased in 3 and remained unchanged in 4 of the 8 subjects in whom valid data on CFC were obtained. These data obtained with pharmacologic agents are in good accord with the findings of Kitchin,³ who has also studied the influence of intra arterial adrenaline on the CFC in the forearm of man. The existence of a dual pathway of blood in forearm muscle is further corroborated by the studies with muscle clearance of KI 131 in cats¹⁰ and in man.⁹

Fend and associates¹⁰ have demonstrated that the emotional increase in forearm blood flow is located exclusively in muscle whereas the tone of cutaneous vessels increases during mental stress and skin blood flow remains unchanged during the rise in blood pressure. It seems to be highly improbable also in view of the relatively low percentage of skin in the forearm that this would be connected with such a drop in cutaneous CFC to override the increase in muscle CFC after the use of pharmacologic agents. In addition acetylcholine actually increases cutaneous blood flow. The argument that our results

were due to opposite changes of CFC in the muscle and skin which cancelled each other out seems therefore to be unlikely.

Thus our data suggest that although in muscular exercise the extra blood entering the working muscle perfuses new capillaries the muscular hyperemia produced by emotion and also by the pharmacologic agents alleged to mediate this hyperemia is accomplished without such new capillaries being opened up. Whether this extra blood passes through some as yet unidentified arteriovenous channels or whether it is simply accommodated by the pre-existing capillaries through which blood flows at a higher speed is impossible to decide on the basis of the present experience.

Summary

1. Capillary filtration coefficient (CFC) in the forearm increases after exercise of the forearm muscle.

2. An increase in blood flow during stressful mental arithmetic comparable in degree to the increase in blood flow after exercise either is not accompanied by any change in CFC or even leads to a drop in the CFC.

3. Adrenaline, acetylcholine and isopropylnoradrenaline which produce an increase in forearm blood flow do not effect any change in the CFC.

We wish to thank Miss B. Beclava and Miss E. Katanová for skilful technical assistance.

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Aortic flow and other hemodynamic responses to the Valsalva maneuver in the dog

Howard Cohen M.D.*
Chicago III

Since the work of Weber in 1851¹ the Valsalva maneuver (VM) has been recognized as a means by which the hemodynamic condition in man or the laboratory animal can be readily altered. The changes are quickly reversible with cessation of the VM.

Exhaling forcibly against the closed glottis produces hemodynamic changes by raising intrathoracic pressure and thus diminishes the intrathoracic blood content and impedes venous return to the right side of the heart. That blood is actually kept out of the thorax during the VM has been conclusively shown by means of P₂ and Diodrast injected into the deep abdominal veins.

The changes in blood pressure which occur when blood flow is temporarily impeded in this way have allowed the gleanings of much information concerning basic physiologic circulatory mechanisms and the effects of drugs and disease states on these mechanisms.²⁻²²

Discussion in this presentation will be limited to the pressure overshoot (PO) of the VM. This pressure overshoot in the systemic arterial system occurs just after cessation of the VM. According to various investigators the PO is abolished by tetraethylammonium chloride²³⁻²⁷ norpinephrine²⁸ previously existing high venous

pressure,⁶ bretylium tosylate hexamethonium,⁹ orthostatic hypotension,²⁹⁻³² significant heart failure,¹⁶⁻¹⁷ significant mitral stenosis,³³⁻³⁷ aortic stenosis,¹⁶ constrictive pericarditis,³⁸ severe pulmonary vascular disease,^{16-18, 37} and occlusion of the common carotid artery.³⁴ Thus the VM has been used as a test to evaluate these drugs and disease states in the laboratory and even at the bedside.

Various mechanisms have been postulated separately or in combination to account for the loss of the Phase IV response of the VM: (1) a venous pressure too high to be effectively impeded by the VM so that no pool of blood will have stagnated and be ready to go through to the left side when the VM is released;⁶ (2) a weakened myocardium which will not respond with forceful contractions to the onrush of the released blood;¹⁶⁻¹⁸ (3) a blunting of the normal reflex peripheral vasoconstriction so that even when the blood pool is passed rapidly through the left side of the heart peripheral resistance is too low to elicit a rise above control blood pressure;³³⁻³⁵ (4) a mechanical obstruction such as a stenotic valvular lesion or severe pulmonary vascular disease preventing the pooled blood from advancing through the left side with enough velocity to effect an overshoot;¹⁶⁻¹⁸ (5) maximal vasoconstrict-

From the Cleveland Clinic Foundation, Cleveland, Ohio. Department of Medicine, Case Western Reserve Hospital, Cleveland, Ohio.
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Address: Mr. Howard Cohen, Cleveland Clinic Foundation, 2930 St. Elizabeth Ave., Cleveland, Ohio 44115.

tion at the onset of the VMI as with nor epinephrine allowing no further vasoconstriction after release of the VMI and thus no overshoot.²²

No one has demonstrated with certainty the actual mechanism of the normal overshoot. One reason for this is that there has not been until recently a good method of measuring instantaneous aortic flow in the intact animal. Without such measurements of flow, it cannot be determined whether the rise in pressure during the pressure overshoot is due to an increase in blood flow or an increase in peripheral resistance (vasoconstriction) or to a combination of the two. Although ganglionic blocking agents abolish the PO, thus in the absence of concomitant measurements of flow, does not prove that the normal overshoot must be based on vasoconstriction. It only means that the normal overshoot might not be seen when marked vasodilatation pre-exists. Flows have been measured with indicator dilution methods⁹ and have suggested that flow is actually decreased during the pressure overshoot implying that the PO is due solely to peripheral vasoconstriction. This method however does not give instantaneous flows and flow values averaged over a period of time cannot be compared with instantaneous pressures in these circumstances. Thus changes in resistance or peripheral vasoconstriction cannot be determined at any given moment in time. Such information can be obtained at least in the laboratory animal by using the electromagnetic flow meter.

The purpose of this study was to determine the simultaneous conditions of blood pressure, blood flow and peripheral resistance in the systemic arterial system during the PO (Phase IV) of the VMI in anesthetized dogs. It will be shown that almost always a flow overshoot accompanies the pressure overshoot and that peripheral resistance may be increased or decreased during the PO of the VMI.

Methods and materials

One hundred sixteen VMIs were induced in 13 mongrel dogs (male and female) weighing from 12 to 18 kilograms anesthetized with sodium pentobarbital in a dose of 25 mg per kilogram. An endotracheal

rubber cannula with a balloon cuff was secured in place and an ordinary blood pressure cuff was placed around the thorax. An aneroid sphygmomanometer was connected by plastic tubing into a single pressure system with the compressed air source, the 2 liter glass reservoir and the endotracheal tube and blood pressure cuff. The reservoir could be filled and then suddenly opened into the entire system so that the resultant pressure was 25 mm Hg. Intra-pulmonary pressure therefore also reached 25 mm Hg. The pressure could be released simply by disengaging the tubing from the endotracheal cannula (see Fig. 1). This system for simulating the VMI is similar to one previously described.²⁴

Arterial pressures obtained through polyethylene catheters inserted via the femoral or carotid artery were recorded on a Sanborn multichannel direct writer. Aortic flows were obtained by placing a Medicon Model M4001 electromagnetic flowmeter probe on the arch of the aorta through an incision in the lower left thorax and the flow was recorded on the Sanborn writer (Fig. 2). Positive pressure artificial respiration was used during surgery. With the flowmeter probe in place the chest was closed airtight; the pneumothorax was reduced through a 20 gauge needle and the animal was allowed to resume spontaneous respiration. Pressure during the VMI was

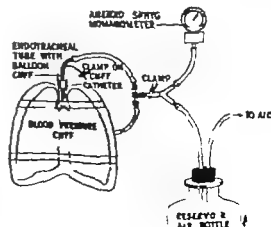


Fig. 1 Diagrammatic representation of the method of inducing the Valsalva maneuver in the closed chest dog. The reservoir or bottle is connected to a compressed air source.

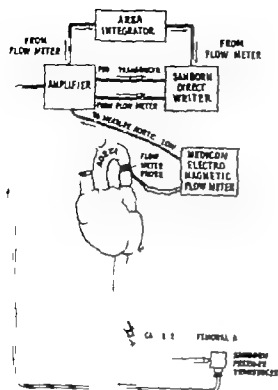


Fig 2 Diagram of the method of measurement. *IP* represents intrapulmonary pressure and aortic flow.

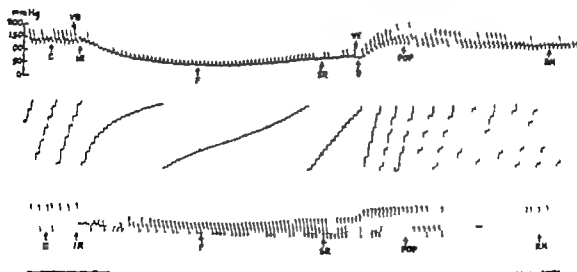


Fig 3 Typical response to Valsalva maneuver. *Top curve* Systemic arterial pressure. *Middle curve* Aortic flow rate. *Bottom curve* Aortic flow rate. *10 mm = 3.750 cc per minute*. *Middle curve* Aortic flow from area of flow rate curve. *3.5 mm = 12 cc of flow*. *C* Control. *IR* Initial rise. *F* Fall during sustained compression. *SR* Secondary rise. *D* Drop with release of Valsalva. *POP* Pressure overshoot period. *RV* Return to normal. *FOP* Flow overshoot period. *1.8 Valsalva begins*. *1.8 Valsalva ends*. Intrapulmonary pressure was 25 mm Hg. Time (bottom line) in seconds.

maintained until arterial pressure began to rise (second part of Phase II of the VM).

Results

Fig 3 shows a typical trial with the Valsalva maneuver.

Of the 116 trials in which systemic arterial flows and pressures were obtained there were 80 in which the typical pressure overshoot was present and 36 in which it was absent. A flow overshoot was detected in 80 trials and was absent in 36 (Tables I and II) (Flow refers to flow per beat.)

Of the 80 trials with a pressure overshoot there were 72 or 90 per cent which had concomitant flow overshoots. Thus in only 10 per cent was the typical pressure overshoot of the VM not associated with an increase in flow.

Of 68 trials with a concomitant peak in instantaneous flow rate overshoot (as distinguished from flow per beat) 30 or 44 per cent had a greater increase in flow than in pressure when expressed as per cent of their respective control values (see

Flow per beat was used to indicate if pressure in flow during the overshoot. Peak (area under curve) flow rate (flow rate) was compared with the corresponding pressure (pressure) during the overshoot period. The overshoot period is the period in time.

Table 1 Summary of trials showing pressure & crush

Induced Valsalva maneuver in the dog	
80 Trials showing pressure overshoot in Phase IV	
Trials with concomitant flow overshoot—72 (90%)	Trials without concomitant flow overshoot—8 (10%)

Table II Summary of trials without pressure overshoot

Indeed Valsalva maneuver in the dog

36 Trials showing no pressure overshoot in Phase IV

Trials with flow overshoot—18 (50%)	Trials without flow overshoot—18 (50%)
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Fig. 10. Percent of total number of trials showing flow overshoot by preceding test. All 8 were of the flow overshoot type.

Table III. Summary of trials showing pressure overshoot.

Trial with concomitant flow rate overaboot—68 (85%)		Trial without concomitant flow rate overaboot—12 (15%)	
<i>Trials</i>	<i>Peripheral resistance</i>	<i>Trials</i>	<i>Peripheral resistance</i>
30 (44%)	Fall	12 (100%)	Rise
34 (50%)	Rise		
4 (6%)	No change		

Table IV Summary of trials without pressure or overshoot

Induced Val-salva maneuver in the dog			
36 Trial showing no pressure overshoot in Phase IV			
Trials with flow rate overshoot—17 (47%)		Trial without flow rate overshoot—19 (53%)	
Trials	Peripheral resistance	Trials	Peripheral resistance
17 (100%)	Fall	16 (84%)	Fall
		1 (5%)	Rise
		2 (11%)	No change

Yes I've control to rest of 1 had number of trials to number of trials on immediately preceding box. All 8 we refer to each to become slow rate

rate. Thus these pressure overshoots were due to an increase in both flow rate and peripheral vasoconstriction. In 4 trials (6 per cent of those with both a pressure and flow rate overshoot) the flow rate and pressure overshoots were equal and denoted no change in peripheral vasoconstriction.⁸

Of the 36 trials with no pressure over shoot 47 per cent showed a flow rate overshoot indicating a peripheral vasodilatation. In the remaining 19 trials both pressure and flow rate fell but to different degrees 16 showed a decreased and 1 showed an increased peripheral resistance and 2 showed no change.

Thus in 116 trials peripheral resistance decreased in 63 or approximately 54 per cent increased in 47 or 41 per cent and remained the same in 6 or about 5 per cent.

Discussion

Classically, the changes in arterial pressure associated with the Valsalva maneuver are divided into four phases. Phase I is a

4. If cost of removal of land subject to trial is more than 1 trial, limited by proceeds of sale. All of the subject land is then sold.

Tables III and IV) This indicates that in these cases there was a decrease in peripheral resistance a vasodilatation. In 34 (>50 per cent of those with both flow rate and pressure overshoots) the pressure increased percentages were more than the flow

[illegible]

short initial rise in pressure immediately after straining has begun Phase II is the subsequent marked drop in pressure followed by a slow rise Phase III is the sudden short drop in pressure when the straining is released Phase IV is the overshoot which is followed by a return to normal Phase I is associated with a bradycardia initiated by the initial rise in pressure Early in Phase II the bradycardia may become more marked possibly because of vagal stimulation by the expanded lungs Later during Phase II there is a tachycardia initiated by low blood pressure and hypoxia With Phase IV a bradycardia occurs which is associated with an overshoot in pressure and a decrease in hypoxia These changes in heart rate indicate the presence of intact sympathetic and parasympathetic pathways

In the present study almost every pressure overshoot was associated with a bradycardia and was preceded by a tachycardia indicating that these autonomic pathways were intact

In those trials in which no pressure overshoot was seen 47 per cent had a flow rate overshoot signifying that the pressure overshoot had been lost solely because of peripheral vasodilatation probably secondary to the anesthesia In the other 53 per cent there was no flow rate overshoot Surgical trauma to the heart great vessels and lungs may have prevented the rapid inflow of blood in Phase IV and explain the loss of the flow and pressure overshoots

The main points brought out in this study concern the 80 trials which demonstrated the classic pressure overshoot In 90 per cent a flow overshoot was present This is in agreement with the classic concepts of these events but contrary to evidence cited when indicator-dilution curves were used

Forty four per cent of the trials showing a concomitant flow rate overshoot showed a decrease in peripheral resistance The data presented here have demonstrated that in the dog under the conditions of these experiments a flow rate overshoot alone can effect the typical pressure overshoot of the Valsalva maneuver This is also suggested by recent work in human beings²⁴

Summary

1 One hundred sixteen Valsalva maneuvers were performed on 13 anesthetized closed chested dogs and recordings were made of aortic flow with an electromagnetic flowmeter and of aortic pressure with catheters threaded into the femoral or carotid arteries

2 Of 36 trials which showed no pressure overshoot during Phase IV half showed a flow overshoot In 47 per cent loss of pressure overshoot was ascribed to peripheral vasodilatation The other 53 per cent showed that a drop in flow rate (or flow rate and peripheral resistance) was the etiology of the loss of pressure overshoot

3 In 80 trials demonstrating a pressure overshoot during Phase IV of the Valsalva maneuver 72 (90 per cent) showed a concomitant flow overshoot Of the 80 pressure overshoots 30 showed a decrease in peripheral resistance during the overshoot

4 This study supports the classic concept that there is a flow overshoot associated with the pressure overshoot of the Valsalva maneuver It also indicates that the pressure overshoot can occur in the face of decreased peripheral resistance in dogs under the conditions of this experiment

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Beta-adrenergic blockade in experimental myocardial infarction

Brian L. Pentecost MD MRCP*

W. Gerald Austen MD**

Boston, Mass

Beta adrenergic blockade by the agent pronethalol or its analogue propranolol has been evaluated clinically in the treatment of angina pectoris^{1,2} and recently its use has been suggested in the management of acute myocardial infarction.³ Inhibition of the positive chronotropic and inotropic effects of sympathetic stimulation on the heart could beneficially result in reduced oxygen requirement of the myocardium after myocardial infarction also the antiarrhythmic properties of pronethalol and propranolol^{4,5} could prevent those serious arrhythmias which frequently claim the lives of patients with relatively small areas of myocardial damage. However beta receptor antagonists reduce myocardial contractility^{6,7} and may in addition inhibit the coronary vasodilator response to anoxia.^{8,9} These effects would be potentially hazardous in the presence of myocardial injury and anoxia after infarction.

The following study was designed to investigate the effect of partial beta adrenergic blockade on the survival rate of dogs submitted to coronary artery ligation. Propranolol was utilized at two dose levels and observations were made to determine the presence of myocardial depression.

Materials and methods

Twenty adult mongrel dogs weighing 10 to 18 kilograms were used. After anesthesia had been induced with intravenous thiopental a cuffed endotracheal tube was inserted and ventilation was maintained by a positive pressure respirator delivering a 50 per cent mixture of oxygen in air. Thoracotomy was performed through a median sternotomy and the pericardium was excised from the anterior aspect of the heart. The heart was rotated to the right for sufficient time to allow dissection of the circumflex artery, round which was placed an untied ligature 5 to 8 mm from its origin. Then the heart was replaced in its normal position in the posterior portion of the pericardial sac. The external iliac artery and vein were cannulated in order to measure central arterial and venous pressures through strain gauge transducers the pressures were recorded continuously on a Sanborn direct writing multichannel recorder. Cardiac output was measured by the Cardio Green method using a Gilford arterial cuvette and a Harvard constant withdrawal pump. The electrocardiogram (ECG) Standard Lead II was recorded from subcutaneous electrodes.

At the outset of each experiment three

From the Department of Surgery, Harvard Medical School, 4th, Corcoran, and Serv. Co. M. M. Bennett, General Hospital, Boston, Mass.

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Physician, Queen Elizabeth Hospital, Birmingham, England. Visiting Research Fellow, Massachusetts General Hospital.

**Associate Professor of Surgery, Harvard Medical School, Associate Visiting Surgeon, Massachusetts General Hospital.

estimations of cardiac output were made over the course of 20 minutes together with pressure and electrocardiographic records at paper speeds of 25 and 100 mm per second before either administration of drugs or coronary ligation. The animals were then treated in one of three ways. In the first group of 7 dogs no propranolol was administered before coronary ligation and these served as a control series. In the second group of 6 dogs propranolol was infused intravenously over 3 minutes to a total dose of 0.2 mg per kilogram and after a 10 minute period further measurements of cardiac output and pressure were made before the circumflex artery was ligated. In the third group of 7 dogs propranolol was infused in a similar manner to a dose level of 0.08 mg per kilogram further measurements of output and pressure were made as in the second group and the circumflex coronary artery was ligated. In all dogs after coronary artery ligation the ECG and arterial and venous pressures were monitored continuously and estimations of cardiac output were made at 1 5 30 45 and finally at 60 minutes after ligation at which latter time the experiment was terminated. In each experiment effective coronary artery ligation was confirmed at the end of the study. When the dog failed to survive after coronary artery occlusion the time and mode of death were noted. Left ventricular work, tension time index and systolic ejection rate were calculated from the available data using Formulas 1-3.* The systolic ejection period in systolic seconds per minute was obtained from the central aortic pressure by measuring the time from the beginning of the upstroke to the incisure and multiplying by the heart rate.

In all calculations of standard deviation the sample number = n-1. The cardiovascular results of infusing propranolol were statistically evaluated by means of a two

sample ranking test. Comparisons of the hemodynamic results of coronary occlusion in the three groups were treated similarly. The significance of survival rates in the three groups after myocardial infarction was assessed by calculating chi squared.

Results

Hemodynamic data recorded at the beginning of each experiment are summarized in Table I. There was no significant difference between the three groups of dogs initially.

Cardiovascular effects of intravenous propranolol. The results of infusion of propranolol were qualitatively similar at the two dose levels (Table II). The heart rate and cardiac output were reduced in all dogs. Only with the high dose infusion was there a significant increase in mean arterial pressure. Left ventricular work was reduced in all but one dog after infusion of propranolol. There was also a significant fall in the tension time index. Although the duration of each systole was increased as a result of beta adrenergic blockade there was no overall change in systolic ejection rate because of the accompanying bradycardia and fall in cardiac output.

Effects of circumflex coronary artery occlusion. All animals showed electrocardiographic evidence in Lead II of myocardial infarction with elevation of ST and subsequent T wave inversion (Table III). There was a significantly increased survival rate among the dogs pretreated with 0.08 mg of propranolol when compared with the control series ($p < 0.05$). Although the survival rate was greater in the dogs treated with the high dose of propranolol than in the control group the difference did not reach statistical significance at the 5 per cent level.

The hemodynamic changes brought about by circumflex artery ligation recorded 1 to 2 minutes after occlusion are

$$\begin{aligned} (1) \text{ Left vent work (5-kg } \frac{\text{ml}}{\text{min}}) &= \frac{\text{C.O.} \times \text{arterial pressure (mm Hg)} \times 1.36 \times 10^6}{1,000} \times \frac{1}{100} \quad (\text{mean } \pm \text{SD}) \\ (2) \text{ Tension time index (mm Hg sec/min)} &= \text{arterial pressure (mm Hg)} \times \frac{1}{100} \times \frac{1}{\text{heart rate (sec/min)}} \\ (3) \text{ Systolic ejection rate (ml/min)} &= \frac{\text{C.O.} \times \frac{1}{100}}{\text{Systolic ejection period (sec/min)}} \end{aligned}$$

Table I Initial hemodynamic data

Group	Number of dogs	Cardiac output (ml/min)		Mean arterial pressure (mm Hg)		Heart rate (beats/min)	
		Average	± S D	Average	± S D	Average	± S D
Controls	7	888	400	96	19	156	24
Propranolol (0.2 mg/kg)	6	905	253	91	14	175	11
Propranolol (0.08 mg/kg)	7	896	790	93	19	145	24

Table II Hemodynamic responses to intravenous propranolol at two dose levels

	Before infusion	After propranolol (0.2 mg/kg)	Per cent change		Before infusion	After propranolol (0.08 mg/kg)	Per cent change	
			Average	± S D			Average	± S D
Cardiac output (ml/min)	905	789	-13	13.0	896	717	-20	9.5
			$p < 0.05$				$p < 0.01$	
Stroke volume (ml)	575	650	+13	12.7	63	66	+4.5	14.4
			$p < 0.05$				$p > 0.10$	
Mean arterial pressure (mm Hg)	91	98.5	+7	9.5	93	98	0	7.5
			$p < 0.05$				$p > 0.10$	
Heart rate (beats/min)	175	12	-30.5	7.4	145	109	-25	5.8
			$p < 0.01$				$p < 0.01$	
Left ventricular work (kg M/min)	1.17	1.04	-7.5	7.1	1.11	94	-15	7.4
			$p < 0.05$				$p < 0.01$	
Tension time index (mm Hg sec/min)	1.940	1.672	-14	11.1	1.949	1.659	-15	10.8
			$p < 0.05$				$p < 0.05$	
Systolic ejection rate (ml/stroke sec)	43.7	46.0	+3	8.00	41.1	40.2	-2	8
			$p > 0.10$				$p > 0.10$	

Table III Mortality within 60 minutes of coronary artery ligation

Group	Number of dogs	Deaths	Time of death (range)
Control	7	6	1 min 30 sec — 4 min 40 sec
Propranolol (0.2 mg/kg)	6	3	4 min — 5 min 40 sec
Propranolol (0.08 mg/kg)	7	1	3 min 45 sec

detailed in Table IV. Animals receiving the higher dose of propranolol showed a significantly greater depression of cardiac output and mean arterial pressure than did the control dogs ($p < 0.05$). The calculated systolic ejection rate and left ventricular work were also more depressed in the animals treated with propranolol ($p < 0.01$). Dogs in the third group (pro

pranolol 0.08 mg per kilogram) generally tended to show hemodynamic results midway between those of the other two groups but these were not significantly different from those encountered in either Group 1 or 2. The reduction in the tension time index was similar in all three groups of dogs.

Of the 4 propranolol treated dogs which

Table IV. Comparison of hemodynamic status of dogs before and 1 to 2 minutes after coronary artery occlusion

	Initial values	Post occlusion values	Per cent change	
			Average	S.D.
Control dogs				
Mean pressure (mm Hg)	97	79	-25	15.3
Cardiac output (ml/min)	885	707	-19.5	13.5
Systolic ejection rate (ml/systolic sec)	44.3	39.6	-10	14.0
Left ventricular work (kg M/min)	1.017	0.704	-33	17.4
Tension time index (mm Hg sec/min)	1.060	1.313	-33	1.0
Isoproterenol (0.2 mg/kg)				
Mean pressure (mm Hg)	91	36	-39	13.5
Cardiac output (ml/min)	903	4.6	-48	20.0
Systolic ejection rate (ml/systolic sec)	46.8	17.5	-41	22.7
Left ventricular work (kg M/min)	1.170	0.369	-67	16.5
Tension time index (mm Hg sec/min)	1.946	1.612	-24	18.7
Propranolol (0.08 mg/kg)				
Mean pressure (mm Hg)	93	1	-73	23.0
Cardiac output (ml/min)	896	393	-34	15.0
Systolic ejection rate (ml/systolic sec)	44.1	37.1	-7	17.0
Left ventricular work (kg M/min)	1.110	0.58	-47.5	2.6
Tension time index (mm Hg sec/sec)	1.900	1.314	-2.7	71.6

died 3 had severe depression of cardiac output and mean arterial pressure 1 to 2 minutes after coronary occlusion. Among the majority of survivors arterial pressure improved after the initial depression. At 60 minutes after coronary occlusion mean arterial pressure among the 9 propranolol treated survivors was 93 per cent of the initial value whereas cardiac output was little changed at 63 per cent of the control level (Fig. 1).

All nonsurvivors developed ventricular fibrillation within 6 minutes of coronary occlusion frequently preceded by ventricular tachycardia. Ventricular ectopic beats were seen frequently in survivors treated with propranolol. 1 dog developed 4:1 atrioventricular heart block and 2 showed evidence of transient intraventricular block.

Discussion

There was a significant improvement in the survival rate among dogs receiving 0.08 mg per kilogram of propranolol. One possible explanation of this finding may be that beta adrenergic blockade modifies the function of the heart in a

manner that reduces the oxygen requirements of the myocardium. In this way myocardial hypoxia around the margins of the infarcted area would be minimized and the consequent ventricular irritability avoided.

Consumption of oxygen by the myocardium has been demonstrated to be determined by the tension developed in the myocardium as expressed by the tension time index¹¹ although it is probably the initial process of generation of pressure¹² and the velocity of contraction¹³ rather than its duration which is the critical factor in determining the oxygen needs of the myocardium. Thoracotomy in the dog results in diminished heart size, lowered cardiac output and mean arterial pressure and tachycardia.¹⁴ Propranolol by slowing the heart rate and leaving the arterial pressure only slightly elevated or unchanged reduced the tension time index of the preparation in spite of a prolongation of each individual systole and therefore probably reduced the oxygen requirement of the myocardium just before coronary artery ligation. Left ventricular work was reduced to a greater extent

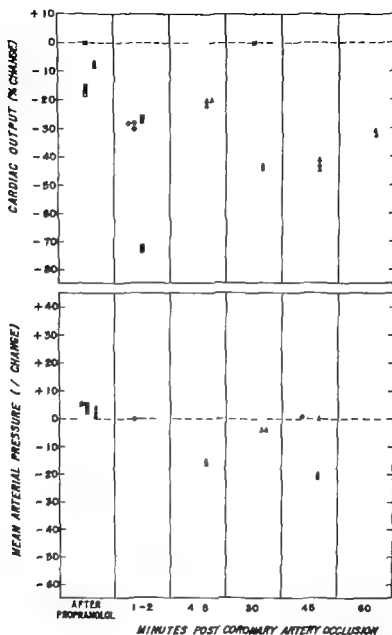


Fig. 1 Changes in cardiac output and mean arterial pressure after infusion of propranolol and circumflex coronary artery occlusion. Open circles: Control nonsurvivors. Open squares: Propranolol 0.2 mg/kg nonsurvivors. Open triangles: Propranolol 0.08 mg/kg nonsurvivors. Solid circles: Control survivors. Solid squares: Propranolol 0.2 mg/kg survivors. Solid triangles: Propranolol 0.08 mg/kg survivors.

than was the tension time index because of the reduction in cardiac output but volume work appears to be of less importance than pressure work in determining myocardial oxygen consumption and coronary blood flow.^{12,13} After coronary artery ligation there was however a similar reduction in the tension time index in all three groups. Thus there is some evidence

that propranolol reduced the oxygen needs of the myocardium before coronary ligation but no evidence of a different hemodynamic response to infarction between the control and low dose propranolol groups. Although the two dose levels of propranolol produced similar results before coronary occlusion the survival rate was significantly improved only in the dogs receiving 0.08

mg per kilogram of propranolol. This finding may depend upon depression of myocardial contractility as a result of greater loss of sympathetic stimulation at the higher dose. Sympathetic stimulation is known to increase myocardial contractility^{19,20} and 3 of the 4 nonsurvivors receiving propranolol showed a profound reduction in cardiac output and mean arterial pressure after coronary ligation. In addition the systolic ejection rate was depressed to a greater degree after coronary ligation in the high dose group than in the other experimental groups.

The high incidence of ventricular fibrillation after coronary artery ligation in this experiment may be related to the tachycardia in the open chest dog which increases myocardial oxygen requirements and the beneficial effects of propranolol may be more difficult to demonstrate in the intact animal. The ability of pronethalol and propranolol to slow the heart rate at rest and during exercise has been shown in man²¹ and a tachycardia after myocardial infarction may be an oxygen-wasting situation correctable by these agents. However in this study the risks of myocardial depression have been shown to be real in 2 animals at the high dose level and in 1 at the low dose level of propranolol. It has been demonstrated that a slow infusion of beta adrenergic blocking agents results in lesser degrees of myocardial depression² than does a rapid injection but the appropriate dose for each individual patient might be difficult to determine.

Alternatively the improved survival rate after propranolol may depend on the antiarrhythmic properties of these drugs. Propranolol has been shown to protect against arrhythmias induced by adrenaline²² and ouabain²³ in the dog, and this property may be independent of its beta adrenergic blocking action.

Summary

Experimental myocardial infarction was produced in dogs by ligation of the circumflex coronary artery. Six of 7 control animals died in ventricular fibrillation within 6 minutes of coronary ligation. Only 1 of 7 dogs which were pretreated with propranolol (0.05 mg per kilogram)

died after the same procedure whereas the mortality rate was not significantly altered by pretreatment with propranolol at a higher dose (0.2 mg per kilogram). There was evidence of greater depression of cardiac function after coronary artery ligation in the dogs receiving the higher dose of propranolol. The mechanism of the protective action of propranolol against ventricular fibrillation in the ischemic myocardium is discussed and its attendant dangers are indicated.

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The prevention by glucocorticoids of endotoxin initiated thrombosis in rat, in relation to fibrinolysis, coagulation, and lipemia

Serge Renaud I V D Ph D

Claude Allard Ph.D.

Jean G. Lalouze M.Sc.¹

Montreal, Canada

Contradictory results have been reported concerning the effect of corticoids on blood coagulation¹ and on atherosclerotic and thrombotic phenomena. In Cushing's syndrome characterized by various hormonal imbalances the unusually severe atherosclerotic lesions have been generally attributed to adrenal hyperactivity. However long term administration of glucocorticoids in man does not appear to cause an increase in aortic atherosclerosis but rather a regression of the intimal lesions. In the rabbit it seems to be well established^{2,3} that the administration of glucocorticoids inhibits the cholesterol induced atherosclerosis although it can increase the cholesterolemia. With regard to thrombosis it has been reported that long term treatment with ACTH or cortisone in man can be followed by thromboembolic complications⁴ although other authors⁵ concluded that the administration of cortisone is rarely followed by thromboembolisms and that cortisone can be given safely to patients with coronary heart disease. In the ham-

ster it seems that cortisone treatment predisposes to platelet thrombosis.¹¹

In recent years¹⁻¹⁰ we have been able to initiate by the injection of gram negative bacteria endotoxins in hyperlipemic rats a thrombotic phenomenon particularly suitable for experimental studies. Since it is briefly mentioned above there is no agreement in the literature concerning the effect of cortical hormones on coagulation and conditions generally associated with atherosclerosis this problem was investigated in the rat in the experiments reported in the present communication. Our studies included the effects of several corticoids on the blood coagulation, the fibrinolytic activity and some lipemic parameters of hyperlipemic rats in which phlebotrombosis was induced by an endotoxin injection.

Materials and methods

In these experiments 254 Holzman male rats with an initial body weight of 140 to 150 grams were utilized. The animals were housed 6 per cage in a constant

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temperature environment and given ad libitum tap water and the following hyperlipemic diet described in detail elsewhere¹⁴: butter 38, casein 11, cellulose¹⁵ 15, cholesterol 5, salt mixture¹ 4, sodium cholate 2, sucrose 23 and vitamin mixture¹ 2 (weight per cent). The animals were fed the diet for 9 weeks (Series I Gr 5 to 8) or 11 weeks (Series I Gr 1 to 4 and Series II and III).

The corticoids were administered in the form of an aqueous suspension at the dose and for the duration indicated in the appropriate table. Heparin was injected subcutaneously after being diluted as follows: Depo-heparin¹⁶ 200 mg, gelatin 2 Gm, dextrose 1 Gm and distilled water quantity sufficient to 24 ml.

At the end of the feeding periods and after 17 hours of fasting a volume of blood corresponding to approximately 1 per cent of the body weight was removed in siliconized syringes from the jugular veins of all of the rats under ether anesthesia. This blood was utilized for determination of the fibrinolytic activity (Series II and III) of the plasma clotting time (Series III) or of the lipemic parameters (Series III).

The fibrinolytic activity was determined in diluted blood according to the technique of Bullimore and collaborators¹⁷ with the following modifications: before sterilization the glassware and needles were siliconized according to the technique reported by Bauer¹⁸. Blood 0.9 ml was drawn into a 2 ml syringe containing 0.1 ml of sodium citrate (3.8 per cent) mixed and then transferred to a tube maintained in crushed ice and containing 17 ml of the phosphate buffer (pH 7.4). In each of 4 screw capped tubes 1 ml of the diluted blood was added to 1.25 units of thrombin in 0.05 ml of physiologic saline. The tubes were inverted twice to ensure mixing, kept for 30 minutes at 4°C, incubated at 37°C and then placed in crushed ice: two of the tubes having been incubated for 1 hour and the other two for 3 hours. The clots were filtered

as described previously¹⁸ on glass cloth washed with 10 ml of cold saline and then placed in tubes in 10 ml of 0.1 N NaOH. The tubes were then incubated for 5 minutes at 100°C and read at 290 mμ in a Beckman spectrophotometer (Model DU) to measure the tyrosine content of the clot. Preliminary experiments under the conditions used here showed that the peak absorption for tyrosine was 290 mμ and that the optical density was inversely proportional to the incubation time particularly between 1 and 3 hours. The fibrinolytic activity is measured by the difference in the optical density between 1 and 3 hours of incubation was expressed in per cent clot lysis and is reported in the tables as such.

The plasma recalcification time in siliconized tubes was determined as follows: all the glassware was siliconized. After a few drops of blood had been drawn for other purposes the syringe was removed and with the same needle 0.9 ml of blood was collected in a syringe containing 0.1 ml of sodium citrate (3.8 per cent). After thorough mixing with the citrate in the syringe the blood was transferred to a centrifuge tube kept at 30°C. After 6 minutes of centrifugation at 2000 r.p.m. the plasma was removed and also kept at 30°C until the test was performed. Experiments to be published elsewhere showed that at this temperature the plasma clotting time remains practically constant for several hours. Next 0.1 ml of the plasma was added to 0.1 ml of sterile physiologic saline and incubated for 10 minutes at 37°C before the addition of 0.1 ml of 0.025 M CaCl_2 . After 1 minute the tube was tilted gently every 10 seconds until a firm clot formed. The test was performed in duplicate. The determinations of cholesterol, triglycerides and lipoprotein in serum were made according to the techniques utilized in previous studies¹⁴.

Immediately after withdrawal of blood for laboratory tests the rats were given by the same needle 1 ml per 100 Gm body weight of physiologic saline containing a *Salmonella typhosa*¹⁹ lipopolysaccharide (0.6 mg per kilogram). The survivors were killed 24 hours after in

¹⁴Upbound Nutrition Laboratories Co.
¹⁵Matheson Chemicals Co. (Nutritional Biochemical Co.)
¹⁶Upbound Nutrition Laboratories Co. (Nutritional Biochemical Co.)
¹⁷Upbound Nutrition Laboratories Co.
¹⁸Upbound Nutrition Laboratories Co.
¹⁹Upbound Nutrition Laboratories Co.

section of the endotoxin autopsy was performed on every animal and the incidence of red hepatic infarcts was recorded.

The macroscopic readings were verified by histologic examination of the left hepatic lobe. As already reported^{22,23} the incidence of hepatic infarcts corresponds exactly to the incidence of occlusive thrombosis.

Results

Series I (Table I) When injected with the *S. typhosa* lipopolysaccharide animals fed the hyperlipemic diet for 11 weeks but otherwise untreated (Gr 1) presented a 100 per cent incidence of multiple red hepatic infarcts resulting from obstruction of the hepatic veins by thrombi and described in detail elsewhere.^{22,23} In addition there was a 16 per cent incidence of anemic renal infarcts due to thrombosis of the interlobar or arcuate arteries and an 88 per cent mortality rate. None of the animals fed the diet for 11 weeks and injected with hydrocortisone (Gr 2) prednisolone (Gr 3) or ACTH (Gr 4) died in the 24 hours after injection of the endotoxin and the incidence of thrombosis varied from 0 to 33 per cent in these groups. The cardiac infarcts which were at the apex or involved a large part of the left ventricle were due to obstruction of a coronary artery by a thrombus

usually at a bifurcation (Figs 1 II and 3). In the animals fed the hyperlipemic diet for 9 weeks but otherwise untreated (Gr 5) injection of the endotoxin induced thrombosis only in the hepatic veins the incidence being 83 per cent. The mortality rate in this group was only 25 per cent. In the remaining groups fed the diet for 9 weeks those treated with hydrocortisone (Gr 6) presented an incidence of thrombosis of only 33 per cent those with fluoro hydrocortisone (Gr 8) an incidence of 50 per cent and those with desoxycorticosterone (Gr 7) an incidence of 83 per cent. In addition although in Groups 6 and 8 no mortality was recorded Group 7 presented a mortality rate of 66 per cent.

Series II (Table II) In this series all the groups were fed the hyperlipemic diet for 11 weeks. In the first part of the series a single injection of distilled water (Gr 1) or prednisolone (Gr 2) was administered to the animals 2 hours before the determination of blood fibrinolytic activity and the injection of endotoxin. The fibrinolytic activity was significantly lower in Group 2 than in Group 1. Although the incidence of infarcts was the same in both groups the mortality rate was 83 per cent in Group 1 but there was no mortality in the group injected with prednisolone.

In the second part of this series (Gr 3-4-5) distilled water (Gr 3) or prednisolone

Table I. Effect of ACTH and some steroid hormones on the production of endotoxin initiated thrombosis.

Group	Number of rats	Feeding period (wk)	Hormone	Infarct incidence (%)			Survival (mean)	Mortality (%)
				Hepatic	Renal	Cardiac		
1	10	11	None	100	16	0	540 ± 96	88
2	6	11	Hydrocortisone (3 mg)	16	16	0	1440 ± 0	0
3	10	11	Prednisolone (1 mg)	0	33	16	1440 ± 0	0
4	7	11	ACTH (4 IU)	16	16	16	1440 ± 0	0
5	12	9	None	83	0	0	1150 ± 153	25
6	6	9	Hydrocortisone (3 mg)	33	0	0	1440 ± 0	0
7	6	9	Desoxycorticosterone (3 mg)	83	0	0	702 ± 210	66
8	10	9	Fluorohydrocortisone (0.2 mg)	50	0	0	1440 ± 0	0

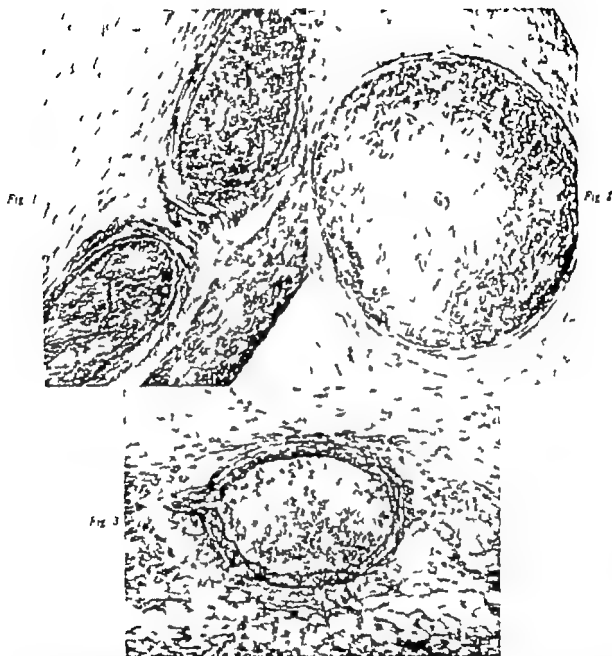
Mean ± S.E.

The rats were injected subcutaneously with endotoxin 48, 24 and 12 hours before the ACTH 22, 48, 60, 24, 16 and 8 hours before the endotoxin.

The animals were fed with the hyperlipemic diet for 11 weeks.

The animals were fed with the hyperlipemic diet for 11 weeks.

The animals were fed with the hyperlipemic diet for 11 weeks.



Figs. 1-3 Histologic appearance at different levels of a thrombus in the left coronary artery of a hyperlipemic rat injected with an endotoxin (periodic acid Schiff $\times 140$). **Fig. 1** The head of the thrombus at a bifurcation. **Fig. 2** The medial part of the thrombus. Note the high distention of the vessel occluded by the thrombus and the resulting stretching of the wall as compared to the same vessel in **Fig. 3**. **Fig. 3** The normal sized coronary artery containing the tail of the thrombus invaded by polymorphonuclear leukocytes.

(Gr 4 and 5) was injected once a day for 4 days (the fibrinolytic activity being determined and the endotoxin administered 2 hours after the last injection). The fibrinolytic activity was still significantly lower in Group 4 than in Group 3. However the

incidence of hepatic infarcts was only 28 per cent in Group 4 as compared with 93 per cent in Group 3. In Group 5, in which in addition to the injections of prednisolone, EACA (1 pylon amino caproic acid) was administered by stomach tube 25

Table 11 Influence of prednisolone on blood fibrinolytic activity and the production of endotoxin initiated thrombosis in hyperlipemic rats

Group	Number of rats	Treatment	% Clot lysis		Infarct incidence (%)			Mortality (%)
			Mean \pm S.E.	p values	Hepatic	Renal	Cardiac	
1	6	Distilled water (1 day)	47 \pm 6		83	16	16	83
2	6	Prednisolone (1 day)	24 \pm 5	<0.02	83	16	0	0
3	14	Distilled water (4 days)	42 \pm 7		93	14	14	83
4	14	Prednisolone (4 days)	19 \pm 5	<0.07	28	14	14	21
5	11	Prednisolone + EACA (4 days)	1 \pm 0.8	<0.01	2	18	0	0

Pred. solo (1 mg) 0.3 ml of distilled water in the same form of distilled water was injected subcutaneously on days 1, 3, 5, 7, 9, 11, 13, 15, 17, 19, 21, 23, 25, 27, 29, 31, 33, 35, 37, 39, 41, 43, 45, 47, 49, 51, 53, 55, 57, 59, 61, 63, 65, 67, 69, 71, 73, 75, 77, 79, 81, 83, 85, 87, 89, 91, 93, 95, 97, 99, 101, 103, 105, 107, 109, 111, 113, 115, 117, 119, 121, 123, 125, 127, 129, 131, 133, 135, 137, 139, 141, 143, 145, 147, 149, 151, 153, 155, 157, 159, 161, 163, 165, 167, 169, 171, 173, 175, 177, 179, 181, 183, 185, 187, 189, 191, 193, 195, 197, 199, 201, 203, 205, 207, 209, 211, 213, 215, 217, 219, 221, 223, 225, 227, 229, 231, 233, 235, 237, 239, 241, 243, 245, 247, 249, 251, 253, 255, 257, 259, 261, 263, 265, 267, 269, 271, 273, 275, 277, 279, 281, 283, 285, 287, 289, 291, 293, 295, 297, 299, 301, 303, 305, 307, 309, 311, 313, 315, 317, 319, 321, 323, 325, 327, 329, 331, 333, 335, 337, 339, 341, 343, 345, 347, 349, 351, 353, 355, 357, 359, 361, 363, 365, 367, 369, 371, 373, 375, 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3803, 3805, 3807, 3809, 3811, 3813, 3815, 3817, 3819, 3821, 3823, 3825, 3827, 3829, 3831, 3833, 3835, 3837, 3839, 3841, 3843, 3845, 3847, 3849, 3851, 3853, 3855, 3857, 3859, 3861, 3863, 3865, 3867, 3869, 3871, 3873, 3875, 3877, 3879, 3881, 3883, 3885, 3887, 3889, 3891, 3893, 3895, 3897, 3899, 3901, 3903, 3905, 3907, 3909, 3911, 3913, 3915, 3917, 3919, 3921, 3923, 3925, 3927, 3929, 3931, 3933, 3935, 3937, 3939, 3941, 3943, 3945, 3947, 3949, 3951, 3953, 3955, 3957, 3959, 3961, 3963, 3965, 3967, 3969, 3971, 3973, 3975, 3977, 3979, 3981, 3983, 3985, 3987, 3989, 3991, 3993, 3995, 3997, 3999, 4001, 4003, 4005, 4007, 4009, 4011, 4013, 4015, 4017, 4019, 4021, 4023, 402

Table III *Influence of corticoids and heparin on various parameters and the production of*

Group	Number of rats	Treatment	Duration of treatment (days)	Clot lysis* (%)	Plasma clotting time* (sec)
1	17	DIST	1	36 ± 8	230 ± 10
2	17	COL	1	7 ± 4	241 ± 12
3	26	DIST	7	23 ± 5	241 ± 13
4	28	COL	7	15 ± 5	334 ± 22
5	14	COL + IACA	7	0.3 ± 0.2	330 ± 18
6	23	DCA	7	35 ± 6	263 ± 16
7	12	Heparin	1	—	463 ± 98

Mean ± S.E.

*a and pre- or postoperative.

DIST Distilled water; COL Hydrocortisone acetate; DCA Desoxycorticosterone acetate.

Hydrocortisone (1 mg) in 0.5 ml of distilled water or the same volume of distilled water alone was injected subcutaneously once a

Thrombolytic activity was determined by the intravenous injection of a 3% tybess lipopolysaccharide 3 hours after the last injection of heparin.

Group comparisons: 1 vs 3, 4 vs 7, 5 vs 3, $p < 0.001$; 6 vs 3, $0.2 < p < 0.3$.Lipopolysaccharide 4 and 7 vs 3, $p < 0.001$.Thrombolytic 4 vs 3, $p < 0.05$.

incidence of thrombosis was reduced from 85 (Gr 3) to 16 per cent by the heparin treatment.

With regard to cardiac or renal infarcts a combined incidence of 9 per cent was recorded in groups 1 and 3, not one single renal or cardiac infarct was found in any of the other groups.

Discussion

From these experiments it appears that the administration of ACTH or of glucocorticoids such as hydrocortisone or prednisolone for 3 to 7 days at the dosage used here not only markedly alleviates the mortality rate but also considerably reduces the incidence of hepatic thrombosis in the rat. These results were obtained over a period of several months and those in Series III are the sum of several experiments. In this last series the results obtained were the most consistent apparently owing to the long duration of the treatments (7 days). In addition no cardiac or renal infarcts were detected in Series III except in groups injected with distilled water in lieu of the test substances.

The fact that a single administration of the glucocorticoids reduced the mortality rate is concordant with the known protective effect of corticoids on endo-

toxic and other types of shock.^{17, 20} However there was no effect on the incidence of thrombosis a finding that constitutes another reason for differentiating in these as in previous experiments²⁴ between the mortality rate which appears to be the result of shock and the incidence of thrombosis.

This protective effect of corticoids against shock and thrombosis appears to be a prerogative of the glucocorticoids at least for those examined here. Fluorohydrocortisone a steroid possessing the two activities was not so effective as hydrocortisone in protecting against thrombosis. In addition desoxycorticosterone a potent mineralocorticoid consistently increased the mortality rate and did not reduce the incidence of thrombosis. However further experiments appear to be needed in this regard since it has been shown that aldosterone can prevent the endotoxin shock in monkeys¹ and mice.²⁵

It has been reported that glucocorticoids increase the blood fibrinolytic activity in man²⁶ but also that ACTH decreases it in the rabbit.²⁴ Here in the rat the fibrinolytic activity was increased by desoxycorticosterone and decreased by hydrocortisone or prednisolone treatment. At any rate the protection afforded by glucocorticoids against thrombosis could not

hepatic vein thrombosis in rats

Cholesterol (mg %)	Triglycerides (mg %)	Lipoproteins (%)	Hepatic infarct incidence (%)	Mortality (%)
541 ± 80	133 ± 17	9.2 ± 0.8	76	64
515 ± 83	120 ± 10	10.5 ± 0.6	81	23
531 ± 61	128 ± 16	9.1 ± 1.1	85	54
575 ± 78	207 ± 37	22.1 ± 2.9†	14	4
—	—	—	21	1
762 ± 110	133 ± 35	7.5 ± 2.8	10	100
641 ± 42	93 ± 5	72.8 ± 0.9†	16	33

† EACA (Esmol 5000-0-0-0-0-0-0) 2.5 mg/kg was given by stomach tube 2.5 hr before the injection of endotoxin and 1 hr after heparin (apoptin 1 hr 25 mg/kg subcutaneously) into the hepatic vein (11 weeks).

have been due to increased fibrinolysis since the administration of EACA which completely blocked the fibrinolytic activity was not able to inhibit the protective effect of the corticoids. The present study also suggests that under certain conditions the fibrinolytic activity can be completely inhibited without necessarily increasing the risks of thrombosis.

The present data confirm our previous findings¹⁴ in that serum cholesterol and triglycerides are of little value in determining a thrombotic tendency at least in the rat. Here the serum triglycerides were increased by cortisone treatment although the coagulability and the incidence of thrombosis was markedly decreased. These experiments also confirm the close relationship already reported between the plasma clotting time in "clotting tubes"¹⁵ the percentage of a lipoproteins^{14, 16} and the incidence of thrombosis.

The effect of glucocorticoids on the production of hepatic thrombosis, the clotting time and the lipoprotein electrophoretic mobility appears to be similar to that of heparin. As previously shown¹⁷ and confirmed here the administration of heparin markedly increases the clotting time and prevents the production of hepatic thrombosis in hyperlipemic rats. It is also

known that in man treatment with heparin induces the production of pre- α lipoproteins.¹⁸ It has been reported that a rise in the α lipoproteins cholesterol occurs in man after the administration of cortisone¹⁹ although other workers have observed alterations in most atherogenic classes of lipoproteins in the rabbit²⁰ but not in man.²¹ However cortisone has been shown to increase the protamine titer in man² and to have a marked effect on the structure and the function of mast cells²² potentially heparin liberators. Although many more experiments are needed to verify such a hypothesis it is possible that glucocorticoids at certain dosages in rat and in man affect coagulation and thrombosis through liberation into the blood of heparin or heparin like substances.

Summary

Administration of ACTH or of glucocorticoids such as hydrocortisone or prednisolone to hyperlipemic rats for 3 to 7 days resulted in a marked protection against the shock and the large hepatic vein thrombosis induced by *Salmonella typhosa* lipopolysaccharide. By contrast a mineralocorticoid such as desoxycorticosterone increased the mortality rate and did not prevent the production of thrombosis. A single injection of gluco-

corticoid did not affect the incidence of thrombosis although it markedly reduced the mortality rate.

The fibrinolytic activity was depressed in glucocorticoids but stimulated by desoxy corticosterone. In addition EACA did not block the protective effects of glucocorticoids on thrombosis although it completely inhibited the fibrinolytic activity.

The preventive effects afforded by glucocorticoids could be related to a marked prolongation of the plasma clotting time and a considerable increase in the percentage of α lipoproteins which migrated even ahead of the albumin zone on paper electrophoresis. These results were similar to those obtained after the administration of heparin.

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Reversible lupus-like illness induced by procainamide

Horton L. London M.D.*

Detroit Mich

Irwin Pincus M.D. F.A.C.P.**

Los Angeles Calif

The first case of lupus-like illness associated with procainamide therapy was reported by Ladd in 1962.¹ Ten additional cases have since been described.²⁻⁹ The following case report is presented as an addition to the literature on an entity which may prove to occur with some frequency.

Case report

B. P., 50-year-old white man, was first treated with procainamide 1.5 Gm daily in January 1962 for symptomatic paroxysmal atrial fibrillation of 4 years duration. In April 1963 approximately 15 months after the onset of treatment the patient began to experience migratory arthralgia involving multiple joints. There was no swelling of the joints, redness or stiffness. The pain improved on salicylates but recurred intermittently over the next 8 months. Past medical history was negative except for transient anemia in childhood and two episodes of thrombophlebitis of the right leg. Family history was negative for rheumatoid arthritis, systemic lupus erythematosus or other collagen diseases.

In December 1963 the patient was examined for the symptoms of uremia and persistent arthralgia. He denied chest pain, rash, fever or significant constitutional symptoms. Physical examination revealed a healthy appearing man. The blood pressure was 120/80 mm Hg. No skin eruptions or lesions were present. No significant lymphadenopathy was found. The heart was not enlarged. No thrill was palpable. Heart tones were normal and no murmurs were heard. The apical rate was 60 with sinus rhythm. The lungs were clear to auscultation and percussion. The abdomen was soft and not tender. No organs or masses were palpable. No swelling of the joints, redness, heat or limitation

of motion was detected. Hemoglobin was 15.8 Gm, hematocrit was 49, sedimentation rate 22 mm per hour. The white blood count was 6400 with 63 per cent polymorphonuclear leukocytes, 6 per cent monocytes, 31 per cent lymphocytes. The blood uric acid was negative as was the latex test for rheumatoid arthritis. Urinalysis was negative for albumin, sugar and cells. Serum time and determinations were 5.7 and 6.3 mg per cent. The precipitation test for C reactive protein was 1+. Serum electrophoresis showed a total protein of 7.1 Gm with 74 per cent albumin, 3 per cent alpha 1, 9 per cent alpha 2, 8 per cent beta and 6 per cent gamma globulin. The LE cell test was positive. X-ray films of the chest, hips, lumbosacral spine, pelvis and feet were normal. The patient was treated with hydrochlorothiazide 400 mg daily. Symptoms improved but arthralgia recurred intermittently. LE cell tests remained positive in February and May 1964. In May 1964 the relationship of procainamide to the lupus-like syndrome was suspected and the medication was discontinued. Within 4 weeks all symptoms in the joints subsided. In August 1964 the LE cell test revealed less than 1 LE cell per 500 neutrophils. In December 1964 the LE cell test was negative. The patient has been free of any symptoms in the joints for 16 months.

Discussion

Various drugs have been implicated in precipitation of lupus erythematosus or a lupus-like illness. The most frequent association has been with hydralazine. The occurrence of the hydralazine syndrome and its severity seem to be related to high dosage over long periods of time. Initial

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*Associate Attending Physician, Inland Empire Medical Hospital of Detroit, Detroit, Michigan. Present address: 4440

Lincoln University, Detroit, Michigan. Address: 18310 Michigan, Detroit, Michigan.

**Associate Clinical Professor of Medicine and Physiology, University of Southern California, Los Angeles, California.

symptoms resemble early rheumatoid arthritis with pain and inflammation in the joints which disappear promptly on withdrawal of the drug. If therapy is continued however other manifestations of systemic lupus erythematosus occur including fever, rash, arthritis, polyserositis, enlargement of lymph nodes and spleen, leukopenia, anemia, elevated serum globulins and false positive serologic tests for syphilis. Positive L.E. cells are found only occasionally. Renal involvement is rarely if ever encountered.¹¹

Anticonvulsant therapy has also been reported to induce a lupus like syndrome with a high frequency of positive L.E. cell tests. Reactions to trimethadione, diphenylhydantoin and methylethylphenylhydantoin have been described.¹² Although the clinical manifestations of systemic lupus erythematosus usually improved or disappeared when anticonvulsant therapy was terminated serologic and serum protein abnormalities persisted in several of the cases reported. Two fatalities from the anticonvulsant lupus like syndrome have been reported.¹³

The relationship of drug therapy to lupus like diseases remains obscure. Indeed the three groups of drugs implicated seem to produce slightly different clinical syndromes. The hydralazine induced lupus syndrome is dose related, completely reversible and has a low incidence of positive L.E. cell tests. The reported cases of procainamide induced syndrome do not seem to be related to dosage or duration of treatment and all have had positive L.E. cell tests. In neither group has renal involvement been demonstrated. Several of the cases described in patients on anticonvulsant therapy showed evidence of clinical or serologic persistence of disease long after the drug had been discontinued. Two cases terminated fatally. One might speculate that in the cases of persistent or progressive disease idiopathic systemic lupus erythematosus may have preceded a convulsive disorder and anticonvulsant therapy was not a factor in the illness.

Several theories of pathogenesis have been considered. The concept that drugs may precipitate or unmask a latent lupus tendency is difficult to accept because of the prompt and complete recovery which

follows withdrawal of the drugs in the hydralazine and procainamide induced disease. One would anticipate spontaneous clinical relapse in at least an occasional case. To our knowledge this has not been described in the drug induced syndrome.

Another possibility is that the drug activates a subclinical defect or deficiency in a fashion similar to that of primaquine and related drugs which precipitate anemia in patients with glucose 6-phosphate dehydrogenase deficiency. If this is the case the underlying fault is yet to be identified.

Finally it is possible that the syndrome described is a drug reaction which mimics but is not systemic lupus erythematosus. One can only stress that in the full blown drug induced disease the entity is indistinguishable from idiopathic systemic lupus erythematosus by present diagnostic methods.

Summary and conclusions

An additional case of procainamide induced lupus like disease is described. Any patient on procainamide therapy who develops arthritis should be studied for this syndrome. Several possible explanations of pathogenesis are considered. The relationship of drug to disease remains obscure.

Addendum

After this article had been submitted for publication one of the authors (B.L.) observed an additional case of procainamide induced lupus syndrome. Mrs. J.D., a 53 year old patient suffering from mitral stenosis secondary to rheumatic heart disease developed pain in the joints and swelling of the fingers, wrists and right elbow 1 month after being placed on procainamide therapy. The L.E. cell test was positive. All symptoms and abnormal findings disappeared within several weeks after cessation of procainamide therapy.

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Idiopathic heart disease associated with pregnancy and the puerperium

John B Johnson MD*

Gulam Hussain Mir MD**

Prospero Flores MD

Marion Mann MD

Washington DC

Idiopathic heart disease associated with pregnancy and the puerperium is uncommon but has been reported sporadically in the American literature since 1937. The actual incidence of this disorder is unknown but it has been reported as 1 in 1,300 deliveries¹ and 1 in 4,000 obstetric admissions by different investigators. The disorder involves primipara as well as multipara. Many of the patients make complete clinical recovery. The syndrome tends to recur with subsequent pregnancies. The mortality rate is not accurately known but has been reported as being between 30 and 60 per cent.^{4,5} The etiology and pathogenesis are obscure. The histopathologic data are limited. Only 26 previous cases with histologic studies have been found in the literature to date.

The purpose of this communication is to present a case of idiopathic heart disease associated with the puerperium in a 14-year-old primipara, the youngest patient so far reported. The disorder in this instance was fatal within 6 months. During this short period the heart rapidly in-

creased in size from normal x-ray silhouette on admission to a 440 gram heart at postmortem. Careful diagnostic and cardiovascular studies were performed on this patient including electrocardiographic angiocardigraphic and hemodynamic evaluations. In addition pericardial myocardial biopsy under local anesthesia was performed early in the illness. The comparative histologic myocardial changes at biopsy and later at postmortem are presented.

Case report

The 14-year-old Negro primipara had always been in good health until the third trimester of pregnancy when she developed episodes of breath and dependent edema.

Five weeks before the prenatal visit this time Nov. 20, 1961, repeated blood pressure of 144/92 mm Hg 1+ dependent edema and + thrombocytopenia. Her hematocrit was 33 per cent, hemoglobin 8.15 Gm per cent. The blood type was A Rh positive and the hemoglobin was AS. She was hospitalized and treated with chlorothalidone. After 7 days of hospitalization the albumin and edema had increased and the blood pressure was 138/84 mm Hg. During the next 6 weeks the urine and blood pressure remained normal but she gained 33 pounds.

The second hospital admission occurred on Jan-

From the Cardiac Vascular Laboratory Department of Medicine and the Department of Pathology, Howard University School of Medicine, Washington, DC. The study was supported, partly by the Service Department of Health Education and Welfare. Received for publication February 10, 1966. Address: Department of Medicine, Howard University School of Medicine, Washington, DC. *Resident, Internal Medicine. **Resident, Internal Medicine.

11 1962 because of the development of generalized edema. The admission blood pressure was 138/94 mm Hg. Both lungs were clear. The heart was not enlarged and was free of murmurs. Her abdomen was unusually large because of the presence of twins and polyhydramnios. On the second hospital day, she developed a temperature of 100.6 F, tachypnea (30 to 34 per minute) and a sinus tachycardia (110 to 140 per minute). The white blood cell count was 18,900, hematocrit 43 per cent, blood urea nitrogen 29 mg per cent, CO₂ combining power 33 volumes per cent, fasting blood glucose 67 mg per cent, serologic test for a phlebotomy and urinary albumin 4+. There was no evidence of disease of the respiratory tract other than a mild tonsillopharyngitis.

With antibiotic therapy the patient's temperature became normal but she continued to have tachypnea and tachycardia until Jan. 15 1962 when she gave birth to twin boys following the induction of labor with Pitocin. Her vital signs returned to normal soon after delivery and she was discharged 4 days postpartum and was reported as doing well. Three days later she was readmitted as an emergency case because of frontal headaches and incoherence. In the Emergency Room she developed grand mal type convulsion and became temporarily comatose. Physical examination on admission revealed a pulse of 120, respiration 40, blood pressure 140/90 mm Hg, normal ocular fundi, decreased bilateral lower lung field rales, gallop rhythm but no cardiac murmurs or peripheral edema. There were no neurologic deficits. The cerebrospinal fluid and skull x-rays were normal. The electroencephalogram was mildly abnormal with a left temporal focus. Five days after admission she developed transient paresis of the right arm and leg and some blurring of vision.

On Feb. 5 1962 (the fifteenth hospital day) the patient complained of a nonproductive cough and developed pulmonary edema. Auscultation showed an accentuated pulmonary second sound, a darkolic gallop rhythm and a questionable pericardial friction rub. A portable x-ray film of the chest indicated cardiomegaly and mild to moderate pulmonary edema. The increasing heart size and pulmonary changes are illustrated in Fig. 1 A and B. There was an 8 pound gain in weight during the 15 days of hospitalization. She was rapidly digitalized and was also given anti-bronch and steroid. The cardiomegaly and tachycardia persisted. A Grade I basal systolic murmur developed on the twentieth hospital day.

Significant laboratory data: SGOT SGPT ASO titer C-reactive protein serum calcium and electrolyte were all normal. White blood cell count 7,800 hemoglobin 10.15 Gm per cent serum albumin 3.4 Gm per cent serum globulin 3.2 Gm per cent and the serum creatinine 2.4 mg per cent. Urinary thematocrit preparations were negative.

The questionable pericardial friction rub enlarging heart size and T wave changes suggested the possibility of pericarditis with effusion. The clinical impression at this time was postpartum pancreatitis of obscure etiology with pulmonary and cerebral embolism.

As the patient's condition stabilized, right heart

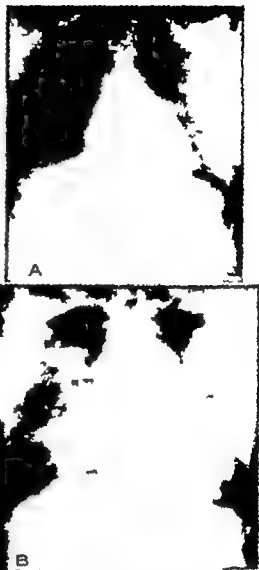


Fig. 1 A. Supine anteroposterior position reveals heart and lungs to be essentially normal. B. Supine anteroposterior projection. Cardiac silhouette is markedly enlarged. Lungs demonstrate typical butterfly pattern of pulmonary edema.

catheterization and angiocardiology were performed. The hemodynamic data are shown in Table I. These findings were interpreted as compatible with biventricular failure, probably of the high output type. Arterial oxygen saturation was slight. The angiocardiology showed consecutive dilatation of the four cardiac chambers, all of which were unusually capacious (Fig. 2 A and B). The interventricular septum appeared to bulge into the right ventricle. There was no evidence of pericardial effusion. She was discharged on March 8 1962 to be readmitted later for pericardial and myocardial biopsy.

She remained reasonably well compensated under ambulatory clinic therapy for heart failure. On May

Table 1 Hemodynamic data obtained by right heart catheterization

Parameter	Patient at rest
Cardiac index ($l/min/m^2$)	3.2
O ₂ consumption ($cc/mm^2/min$)	158
Blood O ₂ saturation (per cent)	
Arterial	93
Mixed venous	58
A-V O ₂ difference (cc/L)	48
Pressure (mm Hg)	
Systemic	90/41
Pulmonary artery	40/23
Right ventricle	
Systolic/diastolic	40/14
End-diastolic/systolic $\times 100$	34
Right atrium (mean)	14
PC pulmonary artery wedge	21
Vascular resistance ($dyne/sec/cm^2$)	
Pulmonary artery	571
Pulmonary arteriolar	130
Systemic	967

In 1967 pericardial and myocardial biopsies were performed under local anesthesia without complications. Fifty milliliters of pericardial fluid was obtained. Smears and cultures showed no bacteria. The pericardial specimen showed considerable thickening with acute fibrous exudate in focal areas (see below). Sections from the myocardium revealed perinuclear hydropic vacuolization of the myocardial fibers and the remaining sarcoplasm showed fragmentation and irregularity of staining (Fig. 3). A specimen from a skeletal muscle showed perivascularitis. The patient was discharged in compensated cardiac state and under digoxin and chlorothalidate therapy.

The fourth hospital admission occurred on June 16, 1967, 3 weeks after discharge with a 3-day history of vomiting, diarrhea and shortness of breath. Pulse was 170 per minute and blood pressure was 120/90 mm Hg. The neck veins were greatly distended. In addition basal pulmonary rales, cardiomegaly, a harsh pansystolic murmur at left sternal border, diastolic gallop rhythm and a questionable friction rub were present. The heart was palpable 1 fingerbreadth below the right costal margin but was not tender. There was no peripheral edema.

Laboratory data: Blood urea nitrogen 43 mg per cent, sodium 135 mEq/L, potassium 4.3 mEq/L, chloride 84 mEq/L, CO combining power 46 volumes per cent, cholesterol 244 mg per cent and calcium 3.9 mEq/L. The chest x-ray film showed persistent cardiomegaly. The venous pressure was 230 mm H₂O.

The electrocardiogram showed low QRS voltage, absent or inverted T waves in the limb leads and discordant T waves in Leads V₁, V₂ (Fig. 4). Serial

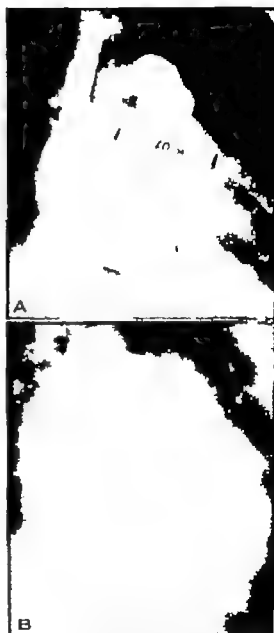


Fig. 2 A Angiocardiogram shows dilated right atrium, right ventricle and pulmonary cones. B Dilated left atrium and left ventricle.

electrocardiograms during the entire illness were remarkable because of the changing electrical axis which terminated in an axis of -90 degrees (Fig. 5).

The possibility of digital intoxication was considered. Digoxin was discontinued with subsequent cessation of the diarrhea. When the drug was resumed 30 mg daily later the patient again began to have loose bowel movements. On the eleventh hospital day she became extremely weak, her pulse was thready and her blood pressure was not ob-



Fig 31 Surgical biopsy of heart revealed degeneration of myocardial fibers. Note vacuoles within the cytoplasm and pyknosis of many of the nuclei. Hematoxylin and eosin $\times 240$.



Fig 32 The inflammatory cells, chiefly lymphocytes, are scattered among remnants of degenerating myocardial fibers. Hematoxylin and eosin $\times 180$.

tainable. Serum electrolyte determinations performed the previous day showed the sodium to be 115 mEq per liter and the chloride 89 mEq per liter. In spite of the administration of intravenous fluid with electrolytes and vasopressor drugs, the patient died on the nineteenth hospital day (July 4, 1967).

At autopsy the heart weighed 440 grams. There were band like adhesions between pericardium and epicardium and many petechiae were scattered over the epicardium. A mural thrombus was attached in the apex and covered the anterior aspect of the left ventricular endocardium.

The progressive nature of this disorder and its fulminant course are well illustrated in the comparative histologic study of the postmortem sections of the heart and the biopsy sections taken 7 weeks earlier. The perinuclear vacuolization, fragmentation, and irregular staining of the muscle fibers in the biopsy specimens have been described above. In the postmortem specimen, extensive destruction of muscle fiber was present with evidence of fibroblastic repair. There were many irregular foci of pale staining muscle fiber remnants consisting of sarcolemmal fragments, pyknotic nuclei, and necrosis (Fig 3B). Budding capillaries, along with fibroblasts, were profuse. Remnants of viable myocardial fibers within and adjacent to the areas of destruction showed evidence of hypertrophy, but



Fig 3C Section through attached mural thrombus. A branch of papillary muscle is embedded in the thrombus at the upper right. Local calcification is seen at lower right. Hematoxylin and eosin $\times 60$.

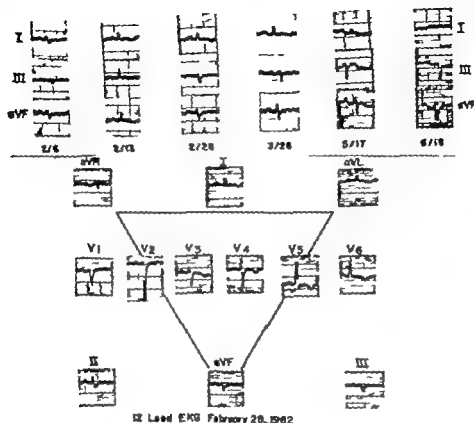


Fig. 4. Serial electrocardiograms demonstrating gradual change in QRS and ST-segment voltage (ST-segment depression and inversion of T in Lead I and V₁).

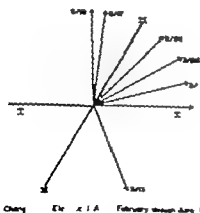


Fig. 5. Diagram illustrating the relationship of changes in QRS and ST-segment in the 12-lead ECG.

are others who have felt that the QRS complex is not a true reflection of the myocardial condition. The QRS complex is a reflection of the electrical activity of the heart, and it is not a true reflection of the myocardial condition.

The QRS complex is a reflection of the electrical activity of the heart, and it is not a true reflection of the myocardial condition.

degenerative changes. The QRS complex and ST-segment changes are not a true reflection of the myocardial condition. There are no recognizable pulmonary emboli. The QRS complex is a reflection of the electrical activity of the heart, and it is not a true reflection of the myocardial condition.

Discussion

We have been able to document 26 autopsied cases of idiopathic heart disease associated with pregnancy and the puerperium to which we added the case of this report. The 27 cases tabulated by age and previous pregnancy are listed in Table II. Two significant features are apparent from this analysis: first, the dominant age group appears to be 30 to 39 years, and second, of the 22 cases for which data were available, 62 per cent were multipara.

It is to be noted from Table III that in 70 per cent of the fatal cases the clinical onset occurred prior to delivery or during the first week post-partum. In nearly half of this group of fatal cases death occurred within 6 months.

The most common clinical man-

Table II Distribution of autopsied cases by age and parity*

Age (yr) at onset	Cases		Cases with previous pregnancies
	Number	Per cent	
14-19	5	18.5	0
20-29	4	14.8	4
30-39	13	48.2	10
Age not stated	5	18.5	2
Total	27	100.0	

*The percentage of the cases studied was 66 per cent. The low incidence of perinatal deaths in this series is related to the observations of these cases.

Table III The onset of symptoms and the duration of life after onset in autopsied cases*

Time of onset	Duration of life after onset			Total
	6 mo	6-12 mo	12 mo	
Before labor	4	1	3	8
First week postpartum	3	0	0	3
Second to twentieth week postpartum	3	1	6	10
Total	10	2	9	21

*The incidence of these cases is low. The percentage of the cases studied was 66 per cent. The low incidence of perinatal deaths in this series is related to the observations of these cases.

tion. The data in Table IV show that dyspnea on exertion, dependent edema, and gallop rhythm occur most frequently in this group of cases. About one third of the patients also showed cough, hemoptysis, persistent tachycardia, abdominal pain, or history of hypertension at onset. Other symptoms were infrequent in this series. When the symptomatology was analyzed with reference to the initial symptoms, dyspnea on exertion was present in 66 per cent of the cases. Although cough and palpitations were not dominant in this series, some authors have reported cough

Table IV Most common clinical manifestations in 22 autopsied cases*

Clinical manifestations	Number of cases	Percentage
Dyspnea on exertion	20	91
Dependent edema		
without anasarca	16	73
Gallop rhythm	14	64
Murmurs	14	64
Abnormal ECGs	11	50
Orthopnea	9	41
History of hypertension (transient)	8	36

*In 5 of the cases, clinical manifestations were not recorded.

and palpitation to be more frequent in these cases than in ordinary cases of congestive heart failure.

The hemodynamic studies in patients with postpartum heart disease have been extremely limited. Other than the case reported herein, we have found only one additional report on the hemodynamics in these patients.¹⁴ At the time of study, our patient was in reasonable cardiac compensation, although the massive cardiomegaly was evident. The circulation time was 15 seconds. As can be seen from Table I, the end diastolic right ventricular pressure was elevated, as was the pulmonary artery wedge pressure, compatible with right and left ventricular failure. The pulmonary vascular resistance was increased. Nevertheless, the cardiac output was within normal limits. We interpreted this to be compatible with a high output type of biventricular failure. These hemodynamic findings are in contrast to those reported by Pierce and associates.¹⁴ In their cases, the cardiac index was greatly reduced, varying from 0.83 to 2.29 L/min/M². They also found an elevation in pulmonary arterial pressure in 2 cases, but the pulmonary wedge pressure was not reported in their paper.

Electrocardiographic studies in this group of 27 cases have been limited, with reports having been listed in only 11 cases. All cases showed low voltage complexes with flat or inverted T waves in most of the leads. Sinus

tachycardia was present in 2 patients, atrial flutter in 1 and left bundle branch block in 2 and in the case which we report a rapidly changing electrical axis from 0 to -90 degrees in a 4 month period (Figs 4 and 5)

Cardiomegaly and mural thrombi

The gross and microscopic pathologies of published cases of postpartum heart disease have been analyzed and compared with the findings in the present case. Cardiomegaly in terms of heart weight was surprisingly great. Of the 24 cases in which the heart weight was reported in only 2 did the heart weigh less than 300 grams. In 18 cases 75 per cent the heart weights were between 350 and 650 grams. Dilated heart chambers were commonly mentioned. In our case at least the greatly enlarged chambers were not merely a terminal event since they were demonstrated by angiocardiography during the early stage of illness. Mural thrombi of the heart were very common being present in 18 of 27 cases (67 per cent). The thrombus was in the left ventricle alone in 8 cases and in multiple chambers in 9 cases usually including the right ventricle. No cases showed coronary occlusion.

Histopathology

The histopathologic findings which other authors have described comprise degenerative, inflammatory and reparative changes which reflect the combined effect of hypoxia, focal ischemia and mechanical or other stresses within the myocardium. The degenerative changes consisted of cloudy swelling, fragmentation, loss of cross striations and irregular staining of muscle fibers along with pyknotic hyperchromatism and karyolysis of nuclei. Hemorrhagic necrosis was occasionally reported. Cellular

infiltration consisted mostly of lymphocytes, mononuclear cells with occasional plasma cells and macrophages. Endocardial thickening and fibrosis were reported in 50 per cent of patients (Fig. 6).

The progressive nature of the myocardial lesion is suggested by the presence of reparative and degenerative changes in the same microscopic field. The rapidity of the progression however is best shown in the histologic picture of the myocardial biopsy specimen from our patient as compared with the histologic picture of the myocardium 2 months later at postmortem (Fig. 3).

The fibrinous pericarditis present in the biopsy specimen in our case is unexplained. There were no histologic changes in the myocardium or elsewhere suggesting active rheumatic pericarditis or lupus erythematosus. Fibrinous pericarditis was not noted in postmortem examination in any of the 27 cases.

Summary

The case of a 14 year old primigravida in whom idiopathic heart disease associated with pregnancy and the puerperium proved fatal 6 months postpartum is presented. Hemodynamic and angiocardiographic studies revealed data compatible with right and left ventricular failure of the high output type and enlargement of all cardiac chambers. The QRS axis of the electrocardiogram showed progressive left axis deviation which seemed to parallel the severity of the disease.

Comparative histologic studies of the myocardial biopsy specimen and 2 months later of the heart postmortem showed evidence of a rapidly progressive widespread degenerative and reparative process in the myocardium.

A review of the American literature reveals only 27 autopsied cases including our case and no previous myocardial biopsies of this disease of obscure etiology.

We have analyzed the 27 autopsied cases with reference to clinical manifestations, electrocardiographic changes, cardiac hypertrophy, mural thrombi and histopathology and most of these cases show striking similarity as reported by different investigators.

Idiopathic heart disease associated with



Fig. 11. Histopathologic changes in the myocardium of 27 autopsied cases of postpartum heart disease.

Table II Distribution of autopsied cases by age and parity*

Age (y) at onset	Cases		Cases with prev. obs. pregnancies
	Number	Per cent	
14-19	5	18.5	0
20-29	4	14.8	4
30-39	13	48.2	10
Age not stated	5	18.5	?
Total	27	100.0	

* 14 of the 27 cases were from the files of the University of California Medical Center, Los Angeles. The remaining 13 cases were from the files of the University of California Medical Center, San Francisco.

Table III The onset of symptoms and the duration of life after onset in autopsied cases*

Time of onset	Duration of life after onset			Total
	0-1 mo	1-12 mo	12 mo	
Before labor	4	1	1	6
First week postpartum	3	0	0	3
Second to twentieth week postpartum	3	1	0	4
Total	10	2	1	13

* 13 of the 27 cases were from the files of the University of California Medical Center, Los Angeles. The remaining 14 cases were from the files of the University of California Medical Center, San Francisco.

tions tabulated in Table IV show that dyspnea on exertion, dependent edema, and gallop rhythm occur most frequently in this group of cases. About one third of the patients also showed cough, hemoptysis, persistent tachycardia, abdominal pains, or history of hypertension at onset. Other symptoms were infrequent in this series. When the symptomatology was analyzed with reference to the initial symptoms, dyspnea on exertion was present in 66 per cent of the cases. Although cough and palpitations were not dominant in this series, some authors¹ have reported cough

Table IV Most common clinical manifestations in 27 autopsied cases*

Clinical manifestations	Number of cases	Percentage
Dyspnea on exertion	20	91
Dependent edema		
without anasarca	16	73
Gallop rhythm	14	64
Murmurs	14	64
Abnormal ECGs	11	50
Orthopnea	9	41
History of hyper- tension (transient)	8	36

* 13 of the 27 cases were from the files of the University of California Medical Center, Los Angeles. The remaining 14 cases were from the files of the University of California Medical Center, San Francisco.

and palpitation to be more frequent in these cases than in ordinary cases of congestive heart failure.

The hemodynamic studies in patients with postpartum heart disease have been extremely limited. Other than the case reported herein, we have found only one additional report on the hemodynamics in these patients.¹¹ At the time of study, our patient was in reasonable cardiac compensation, although the massive cardiomegaly was evident. The circulation time was 15 seconds. As can be seen from Table I, the end diastolic right ventricular pressure was elevated, as was the pulmonary artery wedge pressure, compatible with right and left ventricular failure. The pulmonary vascular resistance was increased. Nevertheless, the cardiac output was within normal limits. We interpreted this to be compatible with a high output type of biventricular failure. These hemodynamic findings are in contrast to those reported by Pierce and associates.¹¹ In their cases the cardiac index was greatly reduced, varying from 0.83 to 2.29 L/min/M². They also found an elevation in pulmonary arterial pressure in 2 cases, but the pulmonary wedge pressure was not reported in their paper.

Electrocardiographic studies in this group of 27 cases have been limited, with reports having been listed in only 9 cases. All cases showed low voltage complexes with flat or inverted T waves in most of the leads. Sinus

tachycardia was present in 2 patients, atrial flutter in 1 and left bundle branch block in 2 and in the case which we report a rapidly changing electrical axis from 0 to -90 degrees in a 4 month period (Fig. 4 and 5).

Cardiomegaly and mural thrombi

The gross and microscopic pathology of published cases of postpartum heart disease have been analyzed and compared with the findings in the present case (Cardiomegaly in terms of heart weight was surprisingly great. Of the 24 cases in which the heart weight was reported in only 7 did the heart weigh less than 300 grams. In 18 cases 75 per cent the heart weights were between 350 and 650 grams. Dilated heart chambers were commonly mentioned in our case at least the greatly enlarged chambers were not merely a terminal event since they were demonstrated by angiocardigraphy during the early stage of illness. Mural thrombi of the heart were very common being present in 18 of 27 cases (67 per cent). The thrombus was in the left atricle alone in 8 cases and in multiple chambers in 9 cases usually including the right ventricle. No cases showed coronary occlusion.

Histopathology

The histopathologic findings which other authors have described comprise degenerative inflammatory and reparative changes which reflect the combined effect of hypoxia, focal ischemia and mechanical or other stresses within the myocardium. The degenerative changes consisted of cloudy swelling, fragmentation, loss of cross striations and irregular staining of muscle fibers along with pyknosis, hyperchromatism and karyolysis of nuclei. Hemorrhagic necrosis was occasionally reported. Cellular

infiltration consisted mostly of lymphocytes, mononuclear cells with occasional plasma cells and macrophages. Endocardial thickening and fibrosis were reported in 50 per cent of patients (Table 6).

The progressive nature of the myocardial lesion is suggested by the presence of reparative and degenerative changes in the same microscopic field. The rapidity of the progression however is best shown in the histologic picture of the myocardial biopsy specimen from our patient as compared with the histologic picture of the myocardium 2 months later at postmortem (Table 3).

The fibrinous pericarditis present in the biopsy specimen in our case is unexplained. There were no histologic changes in the myocardium or elsewhere suggesting active rheumatic pericarditis or lupus erythematosus. Fibrinous pericarditis was not noted in postmortem examination in any of the 27 cases.

Summary

The case of a 14 year old primigravida in whom idiopathic heart disease associated with pregnancy and the puerperium proved fatal 6 months postpartum is presented. Hemodynamic and angiocardigraphic studies revealed data compatible with right and left ventricular failure of the high output type and enlargement of all cardiac chambers. The QRS axis of the electrocardiogram showed progressive left axis deviation which seemed to parallel the severity of the disease.

Comparative histologic studies of the myocardial biopsy specimen and 2 months later of the heart postmortem showed evidence of a rapidly progressive widespread degenerative and reparative process in the myocardium.

A review of the American literature reveals only 27 autopsied cases including our case and no previous myocardial biopsies of this disease of obscure etiology.

We have analyzed the 27 autopsied cases with reference to clinical manifestations, electrocardiographic changes, cardiac hypertrophy, mural thrombi and histopathology and most of these cases show striking similarity as reported by different investigators.

Idiopathic heart disease



Fig. 4 Histopathologic changes in the myocardium in 27 fatal cases of postpartum heart disease.

pregnancy and the puerperium continues to remain in enigma with reference to etiology and pathogenesis

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Electrocardiogram in ventricular rupture after myocardial infarction

Case report

David E. Morton MD*

John H. Gardner MD

George E. McAnimon MD

Pueblo Colo

The odds against recording an electrocardiogram at the time of rupture of the myocardium must be very high. A review of the English literature and consultation with several cardiologists have failed to turn up a single report of such a finding. An electrocardiogram was recorded on a patient who complained of severe precordial pain on the fifth day after a diaphragmatic myocardial infarction and by mere chance the tracing was made at the time of myocardial rupture and the rather sudden death of the patient. Many of the findings were those previously described in the dying heart.¹

Case report

A 54-year-old white woman was admitted to St. Mary's Hospital on April 23, 1964, complaining of severe anterior chest pain which radiated into the left arm. The pain had begun 2 hours previously while she was tending her brother's funeral and was not relieved by three nitroglycerin tablets. She had a past history of treatment for labile hypertension (140/180/76/110 mm Hg) since 1959, an episode of coronary insufficiency in 1960 and severe coronary insufficiency or possibly myocardial infarction in February, 1964. She had been treated for ankle edema with diuretics since 1960. She had had a precordial angina pectoris intermittent-

for several months prior to her current admission and she was on 10 mg hydrocortisone. She had a history of recurrent thrombophlebitis of both legs, an old cholecystectomy, chronic rheumatoid arthritis and an old esophageal hiatal hernia.

Physical examination revealed a slightly obese, very apprehensive woman of 54 years. She was overbreathing and exhibiting carpopedal spasm. The respirations were 30 pulse 110 and regular blood pressure 160/90 mm Hg and temperature 99°F. There was tachycardia of the eyelids. She was slightly flustered and slightly cyanotic. The chest was mildly emphysematous with a few crackling rales scattered throughout both lung fields. The heart was somewhat enlarged to the left. A was louder than P. No murmurs or pericardial friction rub were heard. There were small varicose veins of the leg with signs of old bronch thrombophlebitis and slight pitting edema of both legs. There was mild generalized rheumatoid arthritis.

The prothrombin time was 27 seconds on admission. The blood count and urine were normal. There was no trace of albumin in the latter. The serum GOT was 24 units 12 hours after admission it was 44 units and 24 hours after admission it was 76 units. The cholesterol was 420 mg per cent 3 days after admission. Chest x-ray films were normal except for a retrocardiac density which was thought to be an esophageal hiatal hernia.

A 12-lead electrocardiogram recorded the afternoon after admission showed tachycardia and left bundle branch block and was suggestive of an early diaphragmatic myocardial infarction with elevated S-T segments in Leads II, III and aV₁ (Fig. 1). The ECG recorded

From the Department of Internal Medicine and the Department of Pathology, St. Mary's Hospital, Pueblo, Colo.

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Address: 193 E. Oregon Ave., Pueblo, Colo. 81001.

the day after admission revealed typical changes of a acute diaphragmatic myocardial infarction with Leads III and aVF showing Q waves, elevated ST segments and inverted T waves. Inverted T waves in the precordial leads also suggested some anterolateral myocardial ischemia (Fig. 2).

The patient was given oxygen, morphine, papaverine and trichloromethazine. Bishydroxycoumarin was continued. She responded well to treatment and her blood pressure during the next few days remained around 130/80 mm Hg. Her chest pain dis-

appeared and she felt well. On the evening of the fifth day after admission she suddenly complained of anterior chest pain and within 5 minutes was unresponsive, pulseless without blood pressure and gasping. She was given oxygen and metaraminol but failed to respond and died within 10 minutes. An ECG was recorded just after the patient lapsed into shock and coma and was run continuously until there was no further heart action. It will be discussed below. The clinical impression was diaphragmatic myocardial infarction due to coronary thrombosis and arteriosclerotic heart disease with rupture of the left ventricle and pericardial tamponade.

The terminal tracing (Fig. 3) showed ventricular fibrillation in Lead I then resumption of normal sinus rhythm in subsequent leads with a marked intraventricular conduction defect, the QRS complexes having measured about 0.20 second. In the precordial leads there was a progressive decrease in amplitude of the QRS complexes down to almost nothing. The final continuous strip (Lead V₁) showed a marked first degree heart block (P-R interval of about 0.40 second) which developed in Lead V₆ with continued very low amplitude of the QRS complex. Then the P wave dropped out or changed in configuration. Definite P waves then reappeared with a marked first degree A-V block. Then the QRS waves stopped and only the P waves remained. The QRS waves then returned with marked first degree heart block. Some QRS complexes were followed by an inverted wave of uncertain origin. The QRS waves then came and went intermittently. Then only the P waves remained and finally they disappeared leaving only a straight line which indicated the end of all cardiac electrical activity.

Autopsy findings. The pericardial sac was distended with 400 ml of partly clotted blood. The heart weighed 370 grams. The right ventricular



Fig. 1 Electrocardiogram taken about 7 hours after the symptoms of myocardial infarction had begun suggest a early diaphragmatic myocardial infarction.

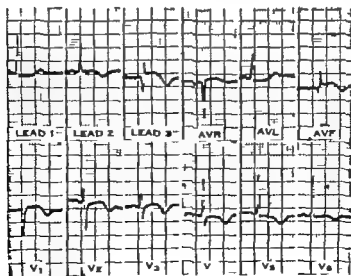


Fig. 2 Electrocardiogram taken the day after the onset of myocardial infarction shows the typical picture for an evolving diaphragmatic myocardial infarction.

chamber was about normal in size. The left ventricular chamber was dilated. Both coronary artery orifices were wide. The right main coronary artery showed moderate arteriosclerosis. It was completely occluded by what appeared to be a fairly fresh dark red thrombus at a level about 3 cm out from the orifice. The left anterior descending coronary artery was moderately narrowed by arteriosclerosis. The left circumflex artery also showed moderate narrowing by arteriosclerosis. No occlusion was found at this level but it appeared to be attenuated with only a few small branches supplying the lateral portion of the left ventricle and it appeared that the posterior portion was supplied predominantly by the right coronary artery. An infarcted area with light yellowish tan coloration and softer in consistency than the adjacent myocardium occupied a region in the posterior basal left ventricular wall about 5.5 cm in greatest diameter. On section the necrosis appeared to involve the posterior basal wall of the left ventricle and the posterior basal portion of the interventricular septum. In the septum it extended anteriorly. In the way to the thin portion of the septum beneath the transverse ring perforation of the myocardium had occurred and an irregular hole extended between the chamber of the left ventricle

and the pericardial sac. There was some dissection across the septum into the posterior muscular wall of the right ventricle as well but the hole which led to the pericardial cavity was situated to the left of the septum. In the epicardium of the heart over its posterior basal surface there was a hematoma about 1 cm thick and 4 cm in diameter (Figs 4 and 5).

All of the sections of the coronary arteries taken for microscopic examination showed arteriosclerosis. The branches from the left artery were narrowed to a variable extent by this. Some cross sections revealed a lumen only about one half of the normal size. Sections of the right coronary artery showed in addition to the arteriosclerosis thrombus material filling the lumen. At some level the thrombus material appeared to be of two different ages with organization apparent at the edge of the older material and with the remainder of the lumen filled with the fresher thrombus material.

Sections from the posterior basal left ventricle and interventricular septum revealed large patches showing changes of subacute myocardial infarction. In these areas the myocardial cell had for the most part disappeared and the patches were made up of loose relatively hypervascular granulation tissue with beginning scar formation. Around the edges of

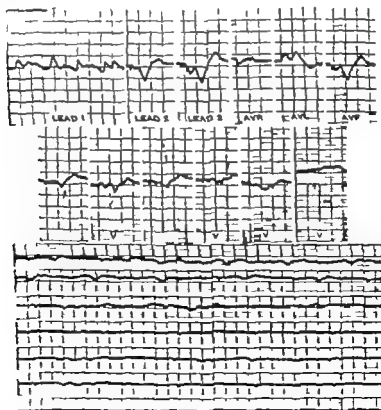


Fig. 3. ECG tracing taken on the fifth day after the onset of myocardial infarction depicts the events just after rupture of the posterior basal portion of the left ventricle and the terminal electrocardiographic changes in the dying heart. See text for details.



Fig. 4 Heart specimen showing (1) an epiauricular hematoma and (2) hemorrhagic necrosis at the edge of the rupture tract in the posterior basal portion of the interventricular septum.



Fig. 5 Heart looking at the septal face of the left ventricle showing a probe passing through the rupture in the posterior basal wall of the left ventricle.

these patches of subacute infarction there were a few patches of more acute necrosis where smudgy pink staining myocardial cells were visible. Most of these lead to their nucleus and striations. At the edges of these more acute necroses were accumulations of polymorphonuclear leukocytes.

Step block sections beginning on the ridge between the foramen ovale and the orifice of the coronary sinus in the right atrium and extending down across the atrioventricular junction into the basal interventricular septum were made to show the conduction system.⁴ The nervous of the septal myocardium extended nearly but not all of the way through to the left endocardial face of the septum. On the right side of the septum necrosis accompanied by inflammatory cells was demonstrated up to and including the endocardial surface. Fig. 6 shows involvement of the subendocardial specialized muscle of the conduction system.

Three different sections taken through the site of myocardial rupture revealed hemorrhage and fibrin clinging to the edges of the tract. The rupture appeared to have occurred through the areas of subacute infarction. The hemorrhage in the myocardial layer was limited to a relatively narrow zone of muscle on either side of the tract of rupture. In the epiauricular fat however it spread out over a broad flat zone of considerable size.

Discussion

A 54 year old white woman with hypercholesterolemia developed a diaphragmatic myocardial infarction despite previous adequate anticoagulation. At some time before the terminal episode the myocardial infarction

extended from the posterior left ventricular wall into the interventricular septum causing the development of the marked intraventricular conduction defect seen on the final tracing (Fig. 3). The gross pathologic findings indicated posterior septal involvement as far forward as the thin portion of the interventricular septum beneath the tricuspid ring. It was not possible to classify definitely the type of intraventricular conduction defect on the terminal electrocardiogram and microscopic examination revealed that both the right and left bundle tissues were damaged especially the right.

The rapidly decreasing amplitude of the QRS complexes from 5 to 1.5 mm in Leads I, II, III, and the precordial leads may have been associated with the dying heart; however this has not been reported generally in the literature. A more likely explanation may be that the rapidly developing hemopericardium which followed the left ventricular rupture produced this picture.

The final continuous strip (Lead VI) recorded the terminal events in the dying heart with first degree heart block, intraventricular conduction defect, intermittent cessation of ventricular complexes, and

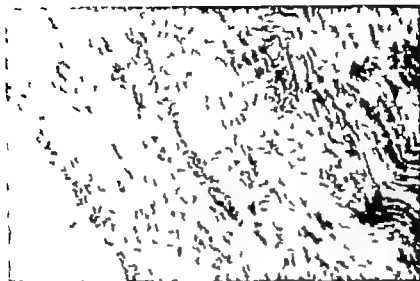


Fig. 6 Microscopic section through the right half of the interventricular septum with the right ventricle cavity on the left of the figure. Myocardial necrosis is shown on the right with leukocytic infiltration extending to the endocardium on the left. Involvement of the long subendocardial Purkinje fibers is apparent. Magnification $\times 80$.

finally disappearance of the P waves with permanent and total cessation of electrical activity in the heart.

Summary

The case of a 34 year old white woman is presented in which an electrocardiogram was recorded at or shortly after the time of rupture of the left ventricle on the fifth day after a diaphragmatic myocardial infarction. The chief features of the terminal electrocardiogram were transient ventricular fibrillation, marked intraventricular conduction defect rapidly decreasing amplitude of the QRS waves, development of first degree atrioventricular block, intermittent cessation of ventricular (QRS) complexes and finally disappearance of atrial activity (cessation of P waves). Autopsy findings gave an excellent correlation with clinical and electrocardiographic findings. As far as can be determined there has been no previous report of electrocardiographic findings at the time of ventricular rupture. Most of the changes described on the terminal electrocardiogram

have been described before in the dying heart and are not diagnostic of myocardial rupture. However the decreasing amplitude of the QRS complexes may have indicated developing hemopericardium secondary to ventricular rupture.

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Clinical pathologic conference

*C H Stuart Harris CBE MD FRCP**

T J Bayley MB ChB MRCP

*Donald Heath MD PhD MRCP***

Birmingham England

Clinical abstract

DR. BAYLEY: The patient was a 67-year-old housewife who had suffered from arthritis since the age of 16 years. This affected her hands, wrists, knees, elbows, shoulders, ankles, and hips in order of decreasing severity. By 1963 the right wrist had become ankylosed. There was ulnar deviation of both hands. There was fixed flexion of both elbows (left 10 degrees of movement, right 10 degrees) and knees (left 5 degrees of movement, right 10 degrees). The feet showed early fibular deviation and there was fixed extension of the right great toe. There were nodules about both elbows. For 6 years she had been treated with a drug, but the dosage of this was reduced in 1964.

When she was 40 years old a swelling on one of her left ribs had been removed. Two years later another swelling from the same site had been removed. When she was 58 years old a radiograph of the heart revealed a shadow in the left hemithorax, a mass was subsequently removed from the left lung.

She was admitted to the hospital on Oct. 6, 1963, at the age of 64 years, with complaints of a throbbing pain in her left loin. She said that for 18 months she had been able to feel a lump on the left side of her abdomen. On examination it was confirmed that she had a mobile ovoid mass 5 by 4 by 3 inches in size in the left hypochondrium. This mass appeared to be firm and smooth with a well-defined margin and the skin was freely movable over it. It was not tender, there was no evidence of pulsation or fluctuation to it, and there was no redness or heat associated with it. On Oct. 17, 1963, this mass was removed at laparotomy. At the time of operation a hiatus hernia was found. She was discharged from the hospital on Oct. 27, 1963.

She was rehospitalized on May 1, 1964, because of increasing pain in her legs. There was evidence of sensory impairment in both feet together with areas of hyperesthesia. No abnormal clinical signs

were found in the chest or abdomen. Her systemic blood pressure was 160/95 mm Hg. Her radial pulse rate was regular at 94 per minute. There was bluish discoloration of the toes. There was no evidence of anemia or lymphadenopathy. She was discharged on June 5, 1964.

She was rehospitalized on Oct. 25, 1965, with complaints that she had been increasingly breathless for 3 months. For 2 weeks she had had rapidly increasing swelling of the legs and abdomen. On examination she was very dyspnoeic even when talking. She had Cushingoid features and purpuric spots. On examination the jugular venous pressure was raised to the angle of the jaw. There was massive edema of both legs and sacral pad. There was free fluid in the peritoneal cavity. There was a rapid irregular tachycardia. On auscultation no murmurs were heard. The systemic blood pressure was 130/80 mm Hg. The trachea was central. There was diminished respiratory movement over the left side of the chest. There was dullness to percussion at the left base posteriorly. Breath sounds were much diminished in this area. On October 27, a left pleural tap was performed but only a few milliliters of fluid were aspirated. She remained very breathless and edematous. Further taps were attempted on October 30 and November 5, but on neither occasion was fluid obtained. She showed no improvement despite intensive treatment. She had no diuretics and became more and more breathless. She became unconscious on November 12 and died 2 days later.

The results of laboratory investigations are given in Table I.

Discussion

PROF. STUART HARRIS: This somewhat unusual patient had polyarthritis for 51 years, died with the signs and symptoms of congestive heart failure, and underwent

From the Medical School University of Birmingham in Birmingham, England. * F.R.C.P. 1944.

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† Mr. George Franklin, Lecturer of Medical Clinic, University of Sheffield.

** Addressee: Department of Pathology, Medical School University of Birmingham, Birmingham B15 2TJ, England.

Table 1 Laboratory investigations

Hemoglobin	71 per cent (May 30 1964) 75 per cent (Nov 12 1965)
White cell count (per cubic millimeter)	9 800 (May 30 1964) 21 400 (Nov 12 1965)
White cell differentials (per cent)	
May 30 1964—Polymorphs	87 eosinophils 1 monocytes 2 lymphocytes 10
Nov 12 1965—Polymorphs	87 eosinophils 1 monocytes 2 lymphocytes 10
Blood urea (mg per 100 ml)	varied between 32 and 63 between Oct 27 1965 and Nov 6 1965
Serum albumin (grams per 100 ml)	varied between 2.8 and 3.0 between Oct 7 1965 and Nov 8 1965
Serum globulin (grams per 100 ml)	varied between 2.6 and 3.4 between Oct 7 1965 and Nov 8 1965
Liver function tests (Oct 26 1965)	
Bilirubin	0.9 mg per 100 ml
Alkaline phosphatase	9.9 units per 100 ml
Thymol turbidity	1 unit
CxSf (May 1 1964) pressure	was 185 mm H ₂ O
Free rise and fall	
Wassermann reaction (Oct 14 1963)	was negative
Pleural fluid (Oct 27 1965)	
No pos cells organisms tubercle bacilli or malignant cells	
No growth of organism on culture	
Bernas meal (Oct 11 1963)	
Very small sliding hiatal hernia with gastro-esophageal reflux	
Blood gases (Oct 26 1965)	
pH 7.49 pCO ₂ 40 mm Hg standard HCO ₃	29 mEq/L

four surgical operations. Since the nature of these operations is not clear at the present I intend to consider first of all the arthritis then the terminal illness and finally the masses in the chest and abdomen that necessitated surgical treatment.

The age of the patient at the time of onset of the arthritis her sex the order of importance of involvement of the joints and the fact that the maximum severity of the arthritis occurred in the hands and wrists leads me to the conclusion that we are dealing here with rheumatoid arthritis. The extreme limitation of movement reported in the joints suggests that fibrous and possibly bony ankyloses had taken place. There is no other disease that can last a lifetime cripple the patient and yet not lead to death excluding that is diseases like psoriatic arthropathy and ankylosing spondylitis. Neither of these latter

diseases would really fit the bill in the present case.

In the last 2 years of her life this patient had complications in the abdomen nervous system and cardiovascular system. All of these are far from common in rheumatoid arthritis. In May 1964 she had increasing pain in the legs with sensory impairment and hyperesthesia in the feet. This appears to have been a peripheral neuropathy and its development in rheumatoid arthritis is highly significant. Even if my own references had let me down the Editor of the *British Medical Journal* published on April 23 of this year a clinicopathologic conference held at the Post Graduate Medical School Hammermith on a patient who also had rheumatoid arthritis and a peripheral neuropathy.¹ There are also a number of papers published on the subject. All agree that such involvement of the nerves indicates the development of an arteritis.² In some ways it resembles polyarteritis nodosa although there may be some obliterative changes and it brings with it a bad prognosis. Such patients have long standing rheumatoid arthritis as in this case they possess subcutaneous nodules and they have high titers of the Rose-Waaler differential agglutinin or rheumatoid factor. The serum electrophoretic pattern is a little different from that of ordinary rheumatoid arthritis. They may or may not have received long term treatment with steroids. I note that the present patient had a long course of therapy and that the dosage of the drug was reduced in 1964 the assumption is that she had been receiving steroids. Before we proceed let me see a radiograph of the hands and know the titer of the Rose-Waaler test. At this stage it might be a good idea to ask you whether lupus erythematosus cells were ever found in this woman.

DR BAILEY: The latex slide test for rheumatoid arthritis was positive. The Rose-Waaler test was also positive to a titer of 128. No lupus erythematosus cells were seen.

PROF STUART HARRIS: I would regard the titer of the Rose-Waaler test as being high. The radiograph of the hands and wrists (Fig 1) shows marked destructive changes in the interphalangeal and metacarpophalangeal joints. The bones



Fig. 1 Rad. graph of hand

some rarefaction with cystic change which may have been of importance at an earlier stage of the disease but which is of no value now in the differential diagnosis between rheumatoid arthritis, gout and the bone lesions of sarcoid. The carpus has undergone fusion. All of these changes are consistent with rheumatoid arthritis and I think that bony ankylosis has occurred in this case.

We are not told of the subsequent history of the peripheral neuritis. It seems to be likely that she would have shown an arthritis in relation to the nerves themselves. In the paper of Hart and Colding² they give a description of a series of cases of polyarthritis with peripheral neuritis. Some of these patients died in cardiac failure, gradually in some cases and suddenly in others.

Now as to the nature of the terminal illness. In October 1965 she had dyspnoea, swelling of the legs, an elevated jugular venous pressure and free fluid in the peritoneal cavity. All of this appears to be right heart failure with edema. She had purpura. She had an irregular cardiac rhythm which I presume was atrial fibrillation and I note that her systemic blood pressure had fallen from 160/95 mm Hg in 1964 to 130/80 mm Hg a year later.

All of these changes might be explained by ischemic changes or even a myocardial infarction or less likely by the endocarditis that may complicate rheumatoid disease. (At this point the ECG was shown.)

Well this ECG confirms that this patient had atrial fibrillation. There is a feeble voltage in the limb leads. I see no evidence of a recent infarction although there are minor changes consistent with ischemia. The swing of the QRS complex is poor and this might indicate damping down by free fluid in the pericardium associated with pericarditis. All in all however there are no major features of intrinsic heart disease in this ECG.

DR BAYLEY: The only other abnormality besides the atrial fibrillation that you have already commented on which was noted at the time was a digitalis effect.

PROF STUART HARRIS: She had purpura. This is not common in congestive cardiac failure but may occur in uremia. However the levels of blood urea recorded are only slightly elevated such as might be found in congestive failure and do not suggest that she has renal failure secondary to stenosis of the renal arteries. Also I note that there are no red cells, protein or casts in the urine.

It would seem that we shall have to look elsewhere for the basis of her terminal illness. This brings us to a consideration of the nature of her lung disease. The description of dullness and diminished breath sounds on the left side of the chest suggests that she had a pleural effusion, but I note that only a few milliliters of fluid were obtained by pleural tap. Of course you can have such an effusion in rheumatoid disease if the lung is affected by interstitial fibrosis or honeycomb change, but I do not think that such lesions were present in this case. Let us see a chest radiograph. (This was shown, see Fig. 2.) Well, there is a large opacity in the left side of the chest. This looks more like an intrapulmonary mass than an effusion to me, and I think that it is likely that we shall have to go back into the history to see whether this is related to the masses in the thorax which were removed previously. I note from the radiograph that the eighth left rib has been removed.

A swelling of this rib was removed when she was 40 years old. Later this mass recurred in the left lung. Subsequently a mass developed in the abdomen. Well, this rib tumor may have been a giant cell tumor or a chondroma, or even possibly an eosinophilic granuloma of bone. However, since the surgeons clearly removed a discrete mass from the left lung, the diagnosis of eosinophilic granuloma is unlikely, because this would be associated

with a more diffuse lesion in the lung. For this reason too I think that it is unlikely that we are dealing with a diffuse fibrosis of the lung. I favor the idea that we are dealing here with a locally invasive mass that began in the rib. Do we have a radiograph of the rib or chest taken when she was 38 years old? (A radiograph of the chest was shown.) Well, this shows a locally invasive mass without diffuse pulmonary change. Before we decide on the nature of this I think that we must consider the abdominal mass. From its description I would say that this could be a localized mass in the peritoneal cavity, possibly a hydatid cyst or a metastasis from the mass in the chest, an enlarged kidney or an enlarged spleen. However, the description is not really consistent with an enlarged kidney, and the mention of pain caused by the abdominal mass is not characteristic of splenomegaly, unless there has been some acute change in the spleen, such as an infarct, a subcapsular hematoma, such as might follow an arteritis or even torsion.

DR BEATTY: We examined this abdominal mass in the pathology laboratory and found that it consisted of plump cartilage cells, some of which were binuclear with a great deal of myxomatous basophilic matrix. The cartilage cells were arranged haphazardly. The appearances were reported as being consistent with a metastasis from a chondrosarcoma.

PROF. STUART HARRIS: This explains the mass in the chest very well. Clearly the original tumors removed were chondromas. I imagine that malignant change took place, and that they recurred locally in the lung, probably by direct spread. Subsequently there was more distant spread by blood or lymphatics.

DR WHITFIELD: Was it possible that this woman had some form of dyschondroplasia, such as Ollier's disease, with secondary sarcomatous change occurring in later life? This would explain the widespread distribution of sarcoma.

PROF. STUART HARRIS: I agree that she has extensive pathology, but we must remember that she lived to the age of 67 years. I am more impressed by the long periods of time in which there was no apparent development of her pathology

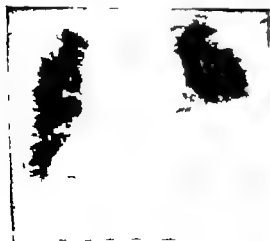


Fig. 2. R. radiograph of the chest taken on Nov. 4, 1965.

I think that it is likely that the spread of sarcoma was from her single rib tumor and not on the basis of malignant change on a diffuse bone pathology like Ollier's disease.

DR SMITH Is it possible that the peripheral neuritis was some sort of neoplastic neuropathy, something akin to carcinomatous neuropathy?

PROF STUART HARRIS It is a possibility but I know of no specific association between chondrosarcoma and neuropathy.

DR HEATH At autopsy this woman showed the typical features of rheumatoid arthritis. The right atrium of the heart was enlarged and infiltrating its muscular wall was a tumor which measured 5 by 4 cm. On cut section (Fig 3) it extended to within 3 cm of the edge of the fossa ovalis. On sectioning the tumor was whitish in color and contained many cysts. A glairy white fluid extruded from it and it was consistent in appearance with being a metastasis of chondrosarcoma. The lower pole of the tumor had ulcerated into the cavity of the right atrium forming a papilliferous mass and superimposed on this was much antemortem thrombus. At first sight the appearances were reminiscent

of an atrial myxoma but the solid cartilaginous appearance revealed its true nature which was subsequently confirmed on histologic examination.

The right ventricle was hypertrophied; this chamber was 5 mm thick and weighed 71 grams. This was subsequently found to be due to tumor emboli in the lungs; many muscular pulmonary arteries were occluded by fragments of chondrosarcoma which had broken off from the friable tumor mass in the right atrium (Fig 4).

There were two deposits of chondrosarcoma in the left lung. One of these was 5 cm in diameter and was situated on the anterior edge of the upper portion of the left lower lobe (Fig 5). On section this



Fig 3 Chondrosarcoma infiltrating the wall of the right atrium.



Fig 4 Tumor emboli (indicated by arrows) in two muscular pulmonary arteries (Hematoxylin and eosin $\times 250$).



Fig 5 The smaller metastasis in the left lower lobe shown in section.

was white in color and contained many small cysts from which a clear glairy fluid could be extruded (Fig 5). There was a second larger tumor mass in the base of the left lower lobe. This was the size of a melon and on cut section showed solid white areas of chondrosarcoma hemorrhage and necrosis (Fig 6).

On histologic examination the appearances were typical of chondrosarcoma. In some areas cartilage cells were readily identifiable although they were haphazardly arranged and some were of bizarre appearance (Fig 7). Most had plump nuclei and some giant cell forms were seen. Some cells were binuclear. Mitotic activity strangely enough was not much in evidence. Between these islands of neoplastic cartilage cells there was much basophilic matrix showing pronounced myxomatous change (Fig 8). Fibrous strands coursed throughout the tumor tissue (Fig 8).

According to authorities such as Lichtenstein and Jaffe¹ when one is deciding the degree of malignancy of cartilaginous tumors the type and distribution of changes in the tumor matrix is unimportant. The important indications of malignancy are the plump and multinuclear nature of the tumor nuclei together with the presence of giant cell forms. Such criteria of malignancy were certainly present in this case.

This case of chondrosarcoma is classic in showing the onset of the tumor in middle life rather than in early life as in osteogenic sarcoma. Furthermore the long drawn out clinical history of local recurrence before the final widespread dissemination of metastases is characteristic thus again contrasting sharply with the behavior of osteogenic sarcoma. The distribution of the metastases to the heart and lungs is also very typical. Lichtenstein and Jaffe¹ point out that the presence of severe respiratory and cardiac symptoms in the terminal illness of a patient with chondrosarcoma may well be a clinical indication of intravascular spread of the tumor with extension to the heart and lungs.

I might add that there was no evidence of systemic rheumatoid disease in the form of rheumatoid aortitis or arteritis or of honeycomb lung. There was also no evi-

dence of Ollier's disease. Do you think that the metastasis of sarcoma in the wall of the right atrium was the cause of the atrial fibrillation?

PROF. STUART HARRIS: Yes I do particularly since the tumor had infiltrated the muscle coat. This case certainly shows that in elderly people we must reject the old aphorism that you must explain all the signs and symptoms on the basis of one pathology. Clearly we need a new aphorism that there are almost certainly

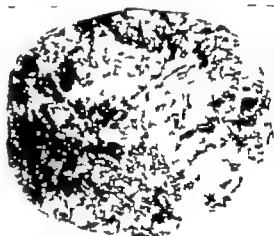


Fig 6 The larger metastasis in the left lower lobe shown in section.



Fig 7 Histologic section of the chondrosarcoma in the wall of the right atrium. Note the plump neoplastic cartilage cell (hematoxylin and eosin, X150).

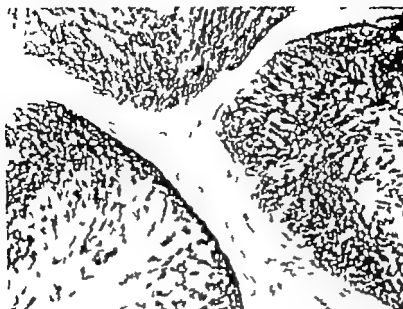


Fig 8 Hologic section of the chondrosarcoma in the wall of the right atrium showing islands of myxomatous matrix separated by strands of fibrous tissue (Hematoxylin and eosin X60)

at least two pathologic processes present by the time one reaches the age of 67 years!

DR IN AM: I think that this case supports the view held by some authorities that if malignancy in a cartilaginous tumor is suspected early resection should be adequate to prevent local recurrence and final widespread dissemination of metastases such as occurred here.

DR ORR: Would you on the other hand agree that ideas on malignancy in chondrosarcoma vary a great deal according to the authority whom you are quoting? My general impression is that we see many cartilaginous tumors in cases in which the degree of malignancy is in doubt. Under these circumstances should our report encourage the surgeons to undertake mutilating operations?

DR IN AM: Lichtenstein and Jaffe⁶ take the view that if the criteria of malignancy that I have referred to earlier are fulfilled then the initial resection should be radical enough to avoid subsequent recurrence. I think that the one exception to this is the chondroma of the hand which is usually benign.

DR ORR: I would certainly agree with that.

DR SINGER: Even so the cartilaginous

tumors are often very pleomorphic. In one and the same tumor one can find some areas that look benign and regular and others that show the more malignant features that are seen in the present case.

DR STUART HARRIS: Have you any experience of tumors of this type arising in tissues other than bone? For example, have you seen them arising from bronchial cartilage?

DR IN AM: Well of course the common cartilaginous tumor of the bronchus is the adenochondroma but I think that we would all regard that as a very benign and quiescent tumor. I have never personally had to deal with a malignant tumor of bronchial cartilage.

DR ORR: Microscopically the tumor of the right atrium in this case looked like a myxoma. Does it suggest that it is a myxoma?

DR IN AM: I do not think that it can be for two reasons. First the histopathology of the tumor is quite unlike that of a myxoma which we have already discussed in one of this series of conferences.⁴ The tumor cells here were definitely cartilaginous in type and did not resemble the stellate cells of the myxoma. Second, I have never heard of a myxoma of the right atrium giving rise to large metastases in

the lungs. As you know, there is a great deal of discussion in the literature about whether a myxoma ought to be considered to be a true neoplasm at all.¹ I have personally seen only one case in which metastatic spread of a myxoma to the lungs was considered to have occurred, and even in that case the invasion through the walls of the pulmonary blood vessels was very early indeed.²

DR. DAYLEY: Well, Professor Stuart Harris, we congratulate you on getting so close to the diagnosis of this difficult case.

Diagnosis: Chondrosarcoma of the right atrium, left lower lobe, and peritoneal

cavity in a woman with rheumatoid arthritis and previously resected chondroma of rib.

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Fundamentals of clinical cardiology

Potentials and limitations of patients after myocardial infarction

George E. Burch M.D.*

Nicholas P. DePasquale M.D.

New Orleans, La.

Although controversy still exists concerning the etiology of coronary heart disease, it is a well accepted fact that by the time most American males reach 50 years of age they have some degree of coronary artery atherosclerosis. Furthermore, although the incidence of most other forms of heart disease has decreased in the last few decades, the incidence of coronary heart disease has increased, at least in the younger age groups. At present, coronary heart disease is probably the most common cause of chronic disability among the working population of the United States. Furthermore, about one third of all deaths in the United States each year are due to acute myocardial infarction.

Patients with coronary heart disease may be divided into three groups on the basis of the clinical findings: viz. (1) those with coronary insufficiency (anginal syndrome), (2) those with myocardial infarction, and (3) those with congestive heart failure. A patient may progress from coronary insufficiency to myocardial infarction and congestive heart failure or may manifest any one or two of the three phases. All of the above mentioned conditions are important causes of absenteeism in the male working population.

The incidence of acute myocardial in-

farction in the general population is difficult to determine. However, it has been estimated that 1 out of every 38 men over 40 years of age and 1 out of every 115 women in the United States has an acute myocardial infarction each year.¹ Although the mean age at the time of the initial myocardial infarction in white males is between 58 and 60 years, the risk of myocardial infarction increases rapidly after 40 years of age. It is during these years that many men reach their peak productivity and hold key positions in industry and the professions. In addition, many men in this age group are heads of households with large financial demands, such as the education of children, the payment of insurance premiums and mortgages, etc. The mortality rate of an initial myocardial infarction in patients between 45 and 60 years of age in many representative large series is about 40 per cent. However, in some series, particularly those from private hospitals, the mortality rate of initial myocardial infarction has been reported to be as low as 5 per cent. Furthermore, life expectancy in men who survive the first myocardial infarction is fairly good, the average being about 10 years in patients who are less than 50 years old and 8.5 years in patients who are over 50 years old.

*F is in the Department of Medicine, Tulane University School of Medicine, and the Charity Hospital of New Orleans, La.

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Address: Department of Medicine, Tulane University School of Medicine, 1430 Tulane Avenue, New Orleans, La. 70112.

at the time of the first infarction. Thus the physician will be faced with the problem of evaluating the capacity to work in at least 6 out of every 10 patients between 45 and 60 years of age who sustain an acute myocardial infarction. This is a difficult task which rests almost completely on the physician in charge of the patient. It is now well recognized that the majority of patients who survive an initial myocardial infarction can be returned to complete or partial employment. However it should be stated at the outset that there are no rules, criteria or tests for evaluating the work capacity of patients after a myocardial infarction which can be substituted for the physician's judgment. To be sure certain tests of function may guide the physician but the ultimate decision in regard to work capacity is one of clinical judgment rather than mathematical or precise criteria.

What is cardiac rehabilitation? The term *rehabilitation* has many meanings. In the minds of most lay people and to many physicians rehabilitation implies some form of physical training to regain or improve a loss of function resulting from disease as for example various exercises in patients with cerebrovascular accidents or paralytic poliomyelitis. In patients with coronary heart disease physical methods may assist the heart to function with the maximum efficiency possible for the anatomic state of the heart but once this point is reached cardiac function cannot be improved by training. There is little reliable information on the value of physical conditioning after myocardial infarction. Experimental studies in dogs have indicated that exercise promotes the development of the coronary collateral circulation after constriction of a coronary artery.⁴ Nevertheless a great deal more needs to be learned about the effect of physical training on cardiac performance in postmyocardial infarction patients before its role in the treatment of coronary heart disease can be evaluated.

Committees established to study the problems of rehabilitation of cardiac patients usually describe the aims of cardiac rehabilitation rather than define what rehabilitation means. These aims usually include restoring the patient's self reliance for the purpose of returning him to his former employment or if that is impos-

sible to employment compatible with his working capacity.⁴ Although these aims are essential to the long term management of patients after myocardial infarction they do not constitute cardiac rehabilitation. In this regard it is important to distinguish between cardiac rehabilitation and rehabilitation of the patient who has had a myocardial infarction. The aims listed above are directed toward rehabilitation of the patient rather than rehabilitation of the heart.

What then is cardiac rehabilitation. In our opinion cardiac rehabilitation in the patient with coronary heart disease consists of the following: (1) preservation as much as possible of the structural integrity of the myocardium through adequate treatment; (2) institution of therapy directed toward establishing the greatest possible coronary collateral circulation; (3) institution of therapy directed toward encouraging compensatory myocardial hypertrophy.

The first two of these are the most important and apply to all patients with heart disease. The third applies primarily to patients with large dilated hearts. It is disturbing to us that so much of the literature on cardiac rehabilitation is concerned with getting the patient back to work, and that there is so little emphasis on preserving and improving the functional state of the cardiac muscle. In the final analysis it is the efficiency of the heart as a pump which will determine the ability to work. It must never be forgotten that the motor of the pump is the myocardium itself. The efficiency of the heart after a myocardial infarction will be determined to a large extent by the adequacy of treatment. Once functional myocardial motor units are dead they can never be regained. Thus in so far as the heart is concerned rehabilitation and treatment are in a great extent the same thing. Obviously the effectiveness of physical training in improving cardiac efficiency will depend upon the amount of healthy myocardial tissue which exists after recovery from infarction. The potentials and limitations of patients after myocardial infarction are therefore greatly influenced by the treatment received during the period of infarction.

The three aspects of cardiac reh-

tion outlined above are discussed briefly below.

Preservation of the structural integrity of the myocardium. After occlusion of a coronary artery a variable amount of myocardial tissue is destroyed. This results in a loss of myocardial motor units so that there is impairment of the heart as a pump. The degree of impairment depends upon the amount of myocardial tissue lost as well as losses accumulated previously from myocardial fibrosis associated with coronary artery disease even in the absence of antecedent clinical myocardial infarction. During the early phases of myocardial infarction the area of injury and ischemia is greater than the ultimate area of death. Thus nonfunctioning but viable myocardial fibers regain their ability to function as a result of physicochemical reparative processes. Therapy should be directed toward insuring recovery of the maximum number of injured muscle fibers. Like any other organ the diseased heart repairs and returns to good health most quickly when it is permitted to rest. Although the heart must continue to work even when it is diseased it is possible within limits to unload and thereby rest the heart by means of relatively simple maneuvers including (1) decreasing the heart rate (2) decreasing the arterial blood pressure (3) decreasing the cardiac output (4) decreasing the size of the heart and (5) decreasing the velocity of myocardial contraction. The physician should review each of these factors in terms of his patient in order to determine which apply to his patient and whether appropriate therapy to modify a given factor has been instituted.

In order to put the heart at rest i.e. reduce the hemodynamic load to a minimum it is not sufficient merely to put the patient with acute myocardial infarction to bed. It is also necessary to recognize and alleviate the psychic disturbances associated with the realization by the patient that he has had a myocardial infarction. This can usually be accomplished by calmness and reassurance on the part of the physician and the judicious use of sedatives. It is also important that the patient be placed in a thermally neutral and comfortable environment. A hot and humid environment increases cardiac work so that

even when the patient is at complete bed rest the heart is not at rest. The importance of this factor is obvious to those who have observed patients with acute myocardial infarction treated during the summer months in hospitals that were not air conditioned. Careful attention must also be paid to such details as providing for small frequent feedings of soft low residue foods making certain that the patient does not develop bladder distention or fecal impaction limiting the number of visitors and eliminating disturbing visitors relieving pain promptly through the use of narcotics and not allowing the patient to be disturbed by so called hospital routine such as bathing the patient changing bed linens and the like. Complacency in the treatment of acute myocardial infarction has developed because of the fact that many patients survive an acute myocardial infarction no matter how they are treated. The point to be emphasized is that the goal of the treatment of acute myocardial infarction should be not only the survival of the patient but also his recovery from the infarction with the least amount of myocardial damage. Many inadequately treated patients do survive but they are often left with a dilated heart congestive heart failure and angina pectoris. This is not to say that adequately treated patients do not have these residuals but only that they are less likely to occur in properly treated patients.

In our opinion the single most important aspect of myocardial infarction in so far as prognosis is concerned is the size of the heart several months after an acute myocardial infarction. The patient who survives a myocardial infarction without developing cardiac enlargement can usually look forward to a productive and relatively symptom free life. On the other hand the patient who develops a dilated heart as a result of myocardial infarction is likely to be seriously handicapped. The mechanical disadvantage of the dilated heart has been discussed previously in papers from this laboratory.¹⁴ It is only necessary to emphasize the fact that whereas the tension in the wall of the normal sized heart decreases or remains constant during systolic ejection the tension in the dilated heart must increase to

support intraventricular pressure. Further more for a given amount of work the greater the myocardial tension the greater the myocardial oxygen consumption and consequently the less the efficiency of the heart.

Instituting therapy directed toward establishing the greatest possible collateral coronary circulation. It is a well established clinical fact that patients with severe angina pectoris may in time experience a decrease in the severity and number of anginal attacks. Presumably improvement is due to the development of the collateral coronary circulation. Further more although it has not been established it has been suggested that coronary vasodilators promote the formation of collateral vascular channels in the myocardium. Patients with severe angina pectoris should be treated with coronary vasodilators and their activity should be limited but not absolutely restricted. Limitation of activity is important if further myocardial damage is to be avoided. On the other hand exercise may contribute to the development of the collateral circulation. Unfortunately there are no criteria by which the physician can determine the amount of exercise that is appropriate for his patient. The amount of exercise prescribed must be based on judgment supported by the physical examination, the subjective response of the patient and the electrocardiographic and roentgenographic findings. Cigarette smoking should be curtailed and completely eliminated if possible. It is probably also wise to restrict the use of caffeine containing beverages. When an adequate collateral circulation develops as is evidenced by a decrease in the frequency and severity of anginal episodes the patient may increase his activity gradually. The fact that angina pectoris is a significant cause of absenteeism as reported in so many studies on the work capacity of patients with coronary heart disease indicates that present attitudes concerning the rehabilitation of cardiac patients need revision. In the long run it is better to delay the return to work of the patient with postinfarction angina pectoris until an adequate coronary collateral circulation has been established than to encourage too early a return to work. Although a patient with angina pectoris

may be able to stay on the job especially if he has a healthy psychologic approach to ward his work permanent disability and retirement may occur earlier than if employment had been delayed and activity restricted. The present aggressive attitude of those involved with the rehabilitation of cardiac patients is disturbing in that too often it appears that the major concern is with getting the patient back to work rather than with what happens to the patient after he returns to work. Nevertheless the physician must temper his judgment with the realization that the longer the patient remains away from his job the more difficult it becomes for him to return to work.

Instituting therapy directed toward encouraging compensatory myocardial hypertrophy. Patients with coronary heart disease extensive myocardial damage and massive cardiac dilatation represent one of the most frustrating problems to the cardiologist. Although patients with large dilated hearts cannot and should not work the physician occasionally encounters such a patient who is strongly motivated to work. In some instances because of the nature of the patient's work for example if he is a top executive or an artist partial return to work may be possible under the physician's careful supervision. However the vast majority of patients with extensive myocardial damage and large dilated hearts should not be permitted to work. Such patients often experience symptoms even at rest. Treatment in general consists of diuretics, digitalis and low sodium diet. In addition the physician is often called upon to treat acute episodes of cardiac asthma, pulmonary edema or myocardial insufficiency. However this therapy is only supportive and the clinical course is one of progressive deterioration.

There is a pressing need to develop methods to improve cardiac function in patients with large dilated hearts. There is pulmonary evidence to indicate that such patients may be improved by prolonged absolute bed rest. Although the value of prolonged bed rest is well established in the treatment of tuberculosis and rheumatic fever it has not generally been applied to patients with coronary heart disease. In fact there is a tendency to en-

courage patients with dilated hearts and chronic congestive heart failure to get out of bed because of an increased risk of thromboembolic disease. It can only be said that the application of present therapeutic concepts have been largely unsuccessful. Unless new forms of treatment are developed, no improvement in the present gloomy outlook for patients with large dilated hearts can be expected. Although placing patients with dilated hearts at absolute bed rest for a year or more in some respects a drastic procedure, the seriousness of the disease requires drastic measures. The dilated heart is under a mechanical disadvantage when compared to the normal sized heart. The tension developed by a given segment of myocardium during systole is related to the intraventricular pressure and the cross sectional area of the ventricle at the level of the segment.¹⁰ During systole the cross sectional area of the normal sized heart decreases so that the product of pressure times cross sectional area is the tension in the myocardial segment either remains unchanged or may actually decrease. Thus the normal sized heart is able to load during systole. On the other hand, the cross sectional area of the dilated heart does not decrease sufficiently during systole to prevent a marked increase in myocardial tension as systole progresses. The increased tension which develops in the wall of the dilated heart imposes an unfavorable load on the dilated heart. This is a physiologic or static load because it is not associated with the movement of blood. Furthermore, the increased tension also imposes a metabolic load on the dilated heart because myocardial oxygen requirement is directly related to tension. Prolonged bed rest is often associated with a decrease in cardiac dilatation. Any decrease in the state of dilatation of the heart automatically unloads the heart to some extent. Theoretically, as the heart is unloaded, improvement in myocardial function results in a further reduction in the dilated state which in turn results in further unloading of the heart and so on until the heart returns to normal size. Of course, this cycle is limited by the degree of myocardial damage. However, as collaterals develop or if one coronary artery is less

narrowed than the other, compensatory localized myocardial hypertrophy may develop in the areas that have a relatively good supply of blood. We have described the hearts of patients in whom one coronary artery was occluded and the other was patent.¹¹ The myocardium in the distribution of the occluded coronary artery was thin and fibrotic and in some instances dilated to the point of formation of an aneurysm. On the other hand, the myocardium in the distribution of the patent coronary artery was markedly hypertrophied. It is reasonable to consider that placing a patient with coronary artery disease and a large dilated heart at complete prolonged bed rest by removing the static and metabolic load from the heart will encourage the gradual development of localized myocardial hypertrophy. Of course, the degree of hypertrophy will be limited by such factors as the extent to which each coronary artery is involved by the arteriosclerotic process and the effectiveness of the collateral coronary circulation.

Rehabilitation of the cardiac patient. As stated above, it is important to distinguish between *rehabilitation of the heart* and *rehabilitation of the patient with heart disease*. The determination of the potentials and limitations of patients with cardiac disease depends primarily upon the evaluation of the patient by his physician. It cannot be done from tables, charts, or by boards of physicians. It is unrealistic first to classify a patient in a certain therapeutic category, and then to look up in a table how much and the kind of work he can do, even when such tables are used only as guides. Tables of energy expenditure during various tasks are subject to large errors, especially when the task is not sedentary. In fact, under certain conditions, it may be virtually impossible to estimate the metabolic cost of a complex task because of the variation in time spent at different phases of the task, each phase requiring a different expenditure of energy. Furthermore, tables of energy expenditure provide information on the total metabolic cost of various activities; they do not indicate the amount of cardiac work performed while carrying out these activities. Nevertheless, it is worth

while for the physician to acquaint himself with such tables of energy expenditure in order to get a general idea of the relative energy costs of various tasks (Fig. 1)

The use of boards of physicians to determine work capacity is a poor practice. No physician, no matter how talented he is, is able to evaluate accurately the work capacity of a patient on the basis of a single examination except perhaps that of patients who are so seriously ill that incapacity is obvious. Members of such boards are usually aware of this fact and for this reason tend to rely heavily on functional tests of cardiac efficiency. At present no test of cardiac efficiency can reliably predict the capacity of a patient to work. When a physician bases his opinion of capacity to work on tests of cardiac efficiency he does the patient an injustice. The physicians on some boards, particularly those in state welfare departments, never see the patient whom they are evaluating

and therefore must base their decision on the physical examinations of other physicians and the comments of a social worker who in most instances they do not know personally. The inadequacy of such a practice needs no comment.

The decision of whether a patient is to return to work after a myocardial infarction, as well as the time and type of work that he is to return to, should be made only by the patient's physician. This is a responsibility of which he cannot divest himself. He may seek the help of a consultant or even a rehabilitation board, but ultimately it is he who must make the final decision. More attention should be paid to informing the practicing physician of the problems in the evaluation of the potentials and limitations of the patient who has had a myocardial infarction and less attention to educating the patient about his infarction. Much of the literature prepared for lay people is filled with oversimplifications

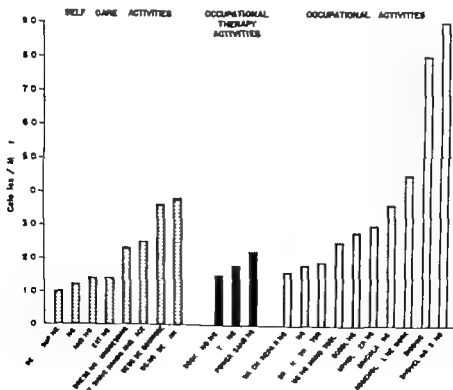


Fig. 1. Average energy costs (in cal/cm² per minute) of various activities in man (Data from Purdue Farm Card Project and Henricson and associates.)

and half truths which confuse the patient. The patient's best source of information is his own physician, not paperback books and brochures.

During the early period of treatment of an acute myocardial infarction the physician will continuously evaluate the severity of the infarct and the response of the patient. He will also evaluate the psychologic effect of the infarction on the patient and his family. As the patient improves he will be gradually allowed to increase his activity until he becomes fully ambulatory. There is no timetable for determining the period of bed rest, sitting in a chair, and finally ambulation. However, it is better to proceed too slowly than too rapidly. During this period the physician will encourage the patient and his family so that when the patient is ready to return to work he will have a good mental outlook. But the physician must be careful. It is just as important for the patient to know his limitations as his potentials. The physician will observe the response of the patient to a progressive increase in activity. On the basis of the physician's impressions and the patient's symptoms, as activity is increased the activity will be adjusted to the patient's capacity. Eventually a sound judgment in regard to work capacity will be reached. This judgment will be based on observations and impressions formed during the entire period of treatment and convalescence. It will include not only the consideration of the patient but that of his family, his employer, and his supervisors; his attitude toward his job and the job itself, as well as many intangibles. A judgment in regard to the potentials and limitations of a patient after a myocardial infarction that is made on any other basis is an unsatisfactory compromise.

Conclusion

At present it appears that about 80 per cent of patients who survive an initial myocardial infarction are able to return to work (Fig. 2). However, among such patients absenteeism due to angina pectoris, congestive heart failure, and cardiac asthma is relatively frequent. In Diamond's study of 348 patients who returned to work after an initial myocardial infarction, 25

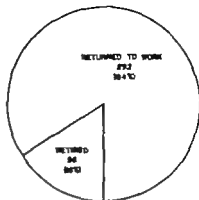


Fig. 2 Fate of 348 men who survived initial myocardial infarction and returned to work. (Data from Diamond.)

per cent sustained a second myocardial infarction within 5 years.³ Thus, although every effort should be made to have patients return to work after a myocardial infarction, the physician must recognize the risks of returning to work too soon as well as the advantages and disadvantages of prolonged inactivity. Until morbidity is reduced, management will continue to be reluctant to employ men who have had a myocardial infarction, particularly for relatively unskilled tasks. The best means of reducing morbidity is adequate treatment during the acute and convalescent phases of the period of myocardial infarction.

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Appraisal and reappraisal of cardiac therapy

Edited by Arthur C DeGraff and Alan F Lyon

Reappraisal of digitalis Part IV Metabolism of the cardiac glycosides

Alan F Lyon M.D.*

Arthur C DeGraff M.D.**

New York N.Y.

There are two major reasons why the use of digitalis remains empirical. The first concerning the uncertainty of its precise physiologic effects has already been reviewed in this series. The second reason is incomplete knowledge of its absorption, distribution, metabolism and excretion. Although there is information concerning a few glycosides in a few animal species, differences between glycosides, differing responses to the same glycosides in different species, and differing responses even in different individuals of the same species are known to exist and cannot be adequately explained. The lack of detailed information despite much ingenious and tedious investigation is due to the difficulty in the identification of the digitalis glycosides and their metabolites in tissue. The total amount of any glycoside in therapeutic dosage in the body at any time is very small and most of this is fixed to tissue. The quantities of digitalis in the blood are therefore infinitesimal and blood levels are of little value in the study of its metabolism. Since digitalis glycosides are steroid compounds quite similar to many natural substances in the body, chemical separation is difficult. Although there are a number of reagents, both acidic and basic, which combine

with the digitalis glycosides and allow precise quantitative determination, none of these is unaffected by other tissue substances and they cannot be used for direct assay in biological systems. On the other hand, bioassay can be accomplished by measuring the effect of a test substance on contractility of cat papillary muscle or on the cardiac rhythm of chick or duck embryo. Finally, isotope assay has been accomplished with two glycosides, digitoxin and digoxin. Digitoxin has been prepared as the C^{14} isotope by isolation from the plant *Digitalis purpurea* grown in an atmosphere containing $C^{14}O_2$. Digoxin is available in the tritiated form that is with tritium substituted for hydrogen. Both the bioassays and isotope assays are extremely sensitive but cannot be used on unprepared tissue samples because of the interference or the toxicity of other substances in the case of the bioassays and because of uncertainty about the persistence of the isotope tag on a cardioactive glycoside in the case of the isotope assays. Therefore in all cases the tissue sample, whether blood, urine or tissue homogenate, must first be prepared by some kind of separation, usually chromatographic, using one or more of the chemical reagents mentioned above and then

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*Chief, Card. Lab. Sect., Veterans Administration Hospital, New York, N.Y.
**Professor of Therapeutics, New York University College of Medicine, 100 East 61st St., New York, N.Y.

elution and measurement. A tremendous amount of work is involved in such studies hence only limited data are available. Although these data agree in trend, there are many presently unreconciled discrepancies in the results obtained by various assay methods. Therefore only an outline of the metabolism of the digitalis glycosides can be presented at this time with any degree of reliability.

There is a marked difference in the metabolism of the clinically used cardiac glycosides depending on their degree of polarity or water solubility. Digoxin is the most studied example of the relatively nonpolar, nonwater-soluble, lipid-soluble glycosides; ouabain at the other extreme is more polar, less lipid-soluble and more water-soluble. Intermediate between these compounds is digitoxin on which a fair amount of information is available.

It is generally agreed that digoxin is almost completely absorbed from the gastrointestinal tract. Ouabain and lanatoside C are poorly absorbed, presumably because they are less lipid-soluble. Another factor that may be operating to interfere with gastrointestinal absorption of many of the strophanthus group and of digitoxin is the destruction of the drugs in the gastrointestinal tract because of greater susceptibility to gastrointestinal enzymes.

Information about the absorption of digoxin is less clear. Prior to the availability of isotope assay, there were various clinical studies, some of which showed digoxin to be equally potent orally and intravenously, and others which seemed to show as much as a 2:1 difference. Studies of tritiated digoxin show that about 90 per cent of digoxin is absorbed but that 20 per cent can be recovered from the stool; the additional 10 per cent resulting from biliary excretion. In one patient who required a large amount of digoxin clinically, 35 per cent of a single dose was found in the stool. Whether this was due to decreased absorption or increased biliary excretion is not known. Such individual variation may account for the discrepancies in previous clinical studies.

Once absorbed into the circulation, all digitalis preparations are widely distributed through the body and rapidly free

to tissue. Nearly complete disappearance from the blood is rapid. The concentration of labeled digoxin given intravenously has been reported to fall to 12 per cent of the initial level at 15 minutes and to less than 5 per cent at 3 hours. Tritiated digoxin given in a single dose intravenously falls to 10 per cent of the initial level after 3 minutes and to 2.8 per cent at 1 hour. The more polar, short-acting glycosides have not been identified one-half hour after a single dose. With the use of precise techniques, a small amount of digoxin continues to be found in the serum with a half-life of 23 hours. This is at a very low level, one fortieth of the tissue concentration, but appears to be in equilibrium with it. Small amounts of digoxin are more easily identifiable in the serum and persist for even longer times. This is due to protein binding, probably to albumin, and may be an important factor in the long duration of action of digoxin.

The distribution of digitalis glycosides to tissues is fairly uniform and does not show any predilection for cardiac muscle. If anything, higher concentrations are recorded in the liver and organs of excretion. C¹⁴ digoxin concentration in the heart has been found to be from 0.5 to 2 times 10^{-6} molar. A partial blood-brain barrier to distribution has been demonstrated at least for digoxin.

The fate of the various digitalis glycosides varies widely. The more polar and clinically shorter-acting ouabain and lanatoside C are excreted rapidly through the bile. It has been reported that 83 to 93 per cent of a single intravenous dose of ouabain and 60 to 85 per cent of a similar dose of lanatoside C could be identified in the bile 5 hours after administration. At the opposite extreme is digoxin, which persists for a long time in the body both as unchanged digoxin (with a half-life of 9 days) and as radioactive metabolites. About 70 per cent of digoxin is metabolized prior to excretion. A considerable portion of this is via hydroxylation to compound C, which has now been identified to be digoxin. Another metabolite not yet identified is called compound B. It is identical to compound B formed from administered digoxin. About 70

cent of digitoxin and its metabolites can be recovered from the urine about 20 per cent in the first 3 days and the rest over a period of 40 days. About 10 per cent of digitoxin is excreted in the bile, some of this is probably reabsorbed but some appears in the stool. Further evidence of the long duration of digitoxin in the body is the persistence of S T segment and T wave abnormalities in the post exercise electrocardiogram of some normal subjects for up to 6 weeks after a single dose of digitoxin.

Digoxin is intermediate in rate of excretion and metabolic degradation. Only about 5 to 10 per cent of digoxin is transformed prior to excretion. Unlike digitoxin which is probably degraded in the liver the metabolic alteration of digoxin takes place primarily in extrahepatic sites. The biologic half life of digoxin is only 1.5 days. About 80 per cent of an intravenous dose is finally excreted in the urine and the remainder in the stool. Thirty seven per cent of a single dose has been reported to be excreted in the urine in the first 3 days and essentially all is excreted in 10 days. This correlates with the electrocardiographic findings that S T segment and T wave abnormalities persist in the post exercise electrocardiogram for only 4 days after a single dose of digoxin.

Clinical importance is attached to the effect of three conditions on the metabolism of digitalis glycosides: these are uremia, severe liver disease and cardiopulmonary bypass. In each instance the present evidence is either fragmentary or to some extent contradictory. In the case of uremia it would appear at least in the case of digoxin that patients with severe renal insufficiency have a reduced rate of excretion. On the basis of these data with some extrapolation it has been suggested that

in patients with blood urea nitrogen of 50 mg per cent or more the maintenance dose of digoxin be reduced to one half or one third of the usual dose. There is no information on the effect of renal insufficiency on the initial loading doses. Studies with tritiated digoxin in patients having hepatic insufficiency have shown no change in the rate of its excretion in the urine or feces or in the partition of metabolites. On the other hand animal studies employing partial hepatectomy showed slow disappearance of ouabain because of interference with excretion and slow disappearance of digitoxin because of slower degradation. The clinical significance of these observations is not clear. The effect of cardiopulmonary bypass on stores of digitalis is also uncertain. It has been shown that no significant amount of digitalis is removed by hemodialysis in uremic patients. Investigators differ about the effect of cardiopulmonary bypass with reports of either no significant change or a modest loss of digitalis. The problem is further complicated by the observation that tritiated digoxin is handled differently from the normal in the post bypass state with a faster turnover initially and then slower turnover.

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Cardiac transplantation without complete cardiac denervation

The role of the afferent receptors

It has been assumed by most authors that total denervation of the heart is an undesirable consequence of cardiac transplantation. It is the intent of this brief review to emphasize that cardiac transplantation can be performed in such a way that major afferent receptors in the heart are preserved. These receptors may play a vital role in maintaining stability of the circulation in the recipient of the heart transplant.

Considerable evidence has now accumulated to indicate that the posterior atrial wall particularly in the atrial-ventricular junctions and the ostia of the pulmonary veins are richly supplied with baroreceptor and organ. The receptors appear to play a significant role in maintaining circulatory homeostasis and fluid volume control by means of neuroendocrine reflexes. The evidence suggests that small changes in intrathoracic blood volume are readily detected by strategic receptors in the atria which transmit vagal impulses to reflexly influence ADH secretion. Other studies have revealed a relationship between atrial stimulation and adrenal cortex secretion. As a result of such neuroendocrine reflexes renal and possibly cardiac compensatory mechanisms maintain a more stable circulatory state. These volume control mechanisms have been comprehensively reviewed by Gauer and Henry.

One method of cardiac transplantation in the dog previously described¹ employs transection of donor and recipient hearts at the level of the atria leaving intact the entire posterior atrial wall in the recipient animal including a ridge of atrial septum. This technique as originally selected as a means for more rapid anastomotic restoration of venous inflow. It is now recognized that a more important result may be the preservation of volume receptor afferent nerve supply. This fact may to a large extent explain discrepancies in the observed incidence of cardiac failure in the postoperative states after cardiac transplantation reported by various investigators. Wilman and associates² early demonstrated the feasibility of survival after total cardiac denervation and after cardiac autotransplantation. Nevertheless they frequently observed the retention of fluid and other manifestations of cardiac failure in the postoperative period. These observations were striking contrast to those of our own group that manifestations of cardiac failure were rare. The major difference

in operative technique which may explain this discrepancy is the more complete preservation of afferent receptors by the method which leaves intact the posterior atrial wall.

Further testing of this hypothesis should be of the utmost importance in selecting the appropriate technique for cardiac transplantation. Confirmation of the role of cardiac afferent receptor may be of equal importance to those designing and investigating the mechanical heart.

Richard R. Lower, M.D.
Associate Professor and Chairman
Division of Thoracic and Cardiac Surgery
Medical College of Virginia
Richmond, Va. 23199

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Fresh nitroglycerin (glyceryl trinitrate)

The controversy over the mechanism of action of nitroglycerin should not be interpreted as an argument over the effectiveness of the drug in the treatment of angina pectoris. Regardless of the mechanism whereby nitroglycerin relieves the pain of coronary ischemia, in our opinion there is little doubt that it does so. Not only should nitroglycerin be readily available to all patients with coronary heart disease; the event of an episode of angina pectoris, but the physician should also recommend its use in prophylaxis. For example, patients should be advised to place nitroglycerin under the tongue before eating or sexual intercourse if these activities frequently precipitate an attack of angina pectoris. It is sometimes forgotten that nitroglycerin is useful in the diagnosis of coronary heart disease. When there is doubt whether a patient is experiencing angina pectoris, the response to nitroglycerin will often provide the diagnosis.

Nitroglycerin is inactivated by time, light, heat, air, and moisture. When a patient reports that nitroglycerin failed to relieve an episode of angina pectoris, it should be suspected that the nitroglycerin was inactive. We have many times observed patients, some of them physicians, who carry nitroglycerin which is many months or even years old in a clear bottle with a metal cap or in a metal pill box. Some patients keep nitroglycerin in the glove compartment of their car where it is subjected to intense heat during the warm months of the year. Patients frequently keep nitroglycerin in a medicine pocket where the heat of the body speed up the deterioration of the drug. Nitroglycerin often fails on the drugstore shelf for many months before it is finally dispensed. Under such circumstances the concentration of nitroglycerin in each tablet is unknown. However, it is certain that it is less than the dose prescribed by the physician. The mere fact that the label on the bottle indicates 1/200 grain of nitroglycerin guarantees only that the manufacturer placed that much nitroglycerin in

each tablet. It does not guarantee that the patient placed 1/200 grain of nitroglycerin under his tongue.

Although many of these facts may appear to be elementary, we are disturbed by the number of patients with coronary heart disease who have not been instructed in the proper handling of nitroglycerin. The responsibility of advising patients on the proper care of nitroglycerin rests on the physician. If more physicians discharged this responsibility, perhaps there would be less discussion about the effectiveness of nitroglycerin in the treatment of angina pectoris. There are so few really effective drugs for the treatment of angina pectoris that patients or physicians must take full advantage of the therapeutic properties of nitroglycerin. Patients should be advised to purchase fresh nitroglycerin (the pharmacist can arrange this). The drug should then be placed in the refrigerator with the exception of a 1 or 2 week supply which is placed in a dark bottle or a plastic container. Before additional nitroglycerin is removed from the refrigerator, the bottle should be allowed to warm to room temperature to avoid condensation of water on cold tablets. The nitroglycerin should be carried in a dark bottle or a plastic container and should not be kept close to the body. The tablets should not be stuffed down with cotton but should be kept in such a manner that the patient can remove them quickly from the bottle.

Nitroglycerin may be a life saving drug. It should be treated as such by physicians and patients alike. An episode of angina pectoris may precipitate a fatal arrhythmia or a myocardial infarction. It is a tragedy when nitroglycerin fails to relieve such an episode of angina pectoris because it is inert.

George F. Burch, M.D.
Nicholas J. DeLongue, M.D.
Department of Medicine
Tulane University School of Medicine
1430 Tulane Ave.
New Orleans, La. 70112

Methysergide and retroperitoneal fibrosis

For the past 5 years methysergide has been used in the management of migraine and other vascular headache more recently it has also been used in the carcinoid syndrome¹ and postgastrectomy states. Side effects are common but usually mild and transient. Occasionally patients have developed arterial vasoconstriction and peripheral ischaemia usually self limited but at times requiring surgical intervention.² Recently more alarming side effects have been ascribed to methysergide therapy. These include retroperitoneal fibrosis and more rarely valvular lesions of the heart and pulmonary inflammation with fibrosis.³

Retroperitoneal fibrosis first described by Ormond⁴ in 1948 is an uncommon condition in which the ureters and other retroperitoneal structures become encased in masses of dense fibrous tissue. Early symptoms are non-specific but may include discomfort in the abdomen or back.⁵ Later the patient may become anuric. Anaemia sometimes of sudden onset may occur but anaemia may be present despite an adequate volume of urine. Since obstructive uropathy is one of the few reversible causes of anuria this possibility should not be overlooked and should be searched for in all cases of renal failure acute or chronic. The diagnosis of retroperitoneal fibrosis is suggested when hydrourephrosis and medial deviation of the ureter are seen by intravenous pyelography. This is confirmed by retrograde studies. Frequently ureteral catheterisation discloses no obstruction and the diagnosis only becomes apparent after dye is injected and the catheter removed. The fibrotic process may also involve other retroperitoneal structures in particular the aorta and its large branches. Such obstruction is not uncommon in such rare cases.

The etiology is unknown. A relationship to other sclerosing conditions such as mediastinal fibrosis sclerosing cholangitis Riedel struma Peyronie disease and Dupuytren's contracture possible and the finding of one of these diseases should lead to a search for the presence of others.⁶ Certain resemblances to the Weber-Christian syndrome suggest that the process originates as an autoimmune disease of adipose tissue.⁷ An autoimmune mechanism is related to systemic lupus erythematosus and other collagen diseases has been postulated because of possible precipitation by immune complexes. In some patients necrotising aortic lesions have been found within the fibrotic tissue.

A direct causal relationship between methysergide and the development of retroperitoneal fibrosis has not been proved. Nevertheless the incidence of this rare disease has increased in recent years of Graham recently reported 2 cases of retroperitoneal fibrosis in patients treated with methysergide. A spontaneous remission occurred in all cases after cessation of therapy which meant that such a development can hardly be fortuitous.⁸

The mode of action of methysergide is not clearly

understood but may involve antagonism of serotonin or serotonin's peripheral action on blood vessels or perhaps a central hypothalamic effect.⁹ Methysergide apparently has no direct vasoconstrictor effect but can potentiate endogenous and exogenous vasoconstrictor substances such as catecholamines nicotine and ergotamine. Patients who suffer from migraines have a generally increased vascular response to vasoconstricting stimuli.¹⁰ Some of these patients also frequently take ergot preparations a synergistic action may occur.

Spontaneous remission has so far occurred in all patients in whose treatment with methysergide was stopped. However we have recently observed a patient in whom the condition appeared to develop or progress over a period of 6 months after cessation of therapy. It may well be that in susceptible subjects methysergide triggers a process which becomes self-perpetuating.

In view of these developments we would suggest the following approach to the patient with retroperitoneal fibrosis when methysergide is involved. Formerly many patients were subjected to early surgical correction. We may now expect that spontaneous regression will occur in most cases after withdrawal of the drug. In addition treatment with steroids may be of benefit in arresting the fibrosis, previous periodic follow up examination is essential however because the process may progress and ultimately require surgical intervention.

Furthermore we suggest that methysergide be used with great caution. Graham recommended that the drug should be avoided in patients with cardiovascular disease as well as in pregnant patients and those with liver and renal disease, connective tissue disorders and a collagen-disease diathesis. Treatment should be intermittent rather than continuous and periodic physical examination and assessments of renal function should be made. At the time the treatment of Akilpanak is quite appropriate. Although migration is not well regarded as fatal disease it may be a real danger to life at least by means of autogenic activities.

Franklin D. Silverman MD
George D. and M.D. M.R.C.P. M.R.C.P.E.
Robert M. Lamb F.R.C.P. F.I.C.P.
Department of Medicine
University of Illinois College of Medicine
and Presbyterian-St. Luke's Hospital
1733 West Congress Parkway
Chgo. Ill 60611

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Research equipment for use in technically developing regions

The physical equipment for research involving electrocardiography in a technically developing region should be as simple as possible. It would be well to take along a new portable battery run transistorized electrocardiograph unit and a supply of 1.5 volt zinc-carbon and electrode jelly appropriate for that unit.

A generalized flattening and dwarfing of complexes in African children was repeatedly noted in many instrument recordings. This in medical units in both East and West Africa. At first the tracings were thought to reflect severe myocardial and/or pericardial disease possibly due to one of the problems common to the tropical electrolyte imbalance protein-calorie malnutrition tuberculosis chronic anemia and endomyocardial fibrosis. However well-nourished vigorous young men with congenital lesions such as patent ductus arteriosus and ventricular septal defect had relatively flat tracings. A battery run unit, the Cambridge Transrite III was obtained and comparative tracings were made using a single set of electrodes connected first to the main instrument and then to the battery run unit. Tracings from the main instrument

were consistently more flattened and dwarfed than those from the battery run unit. It is believed that the error for the lower amplitude of the complexes in the tracing from the main instrument might have been due to low input impedance.

The possibility of low impedance in other equipment, the lack of outside mains in some locations, the unavailability of the electrical power supply and the difficult terrain make an easily portable battery run model especially attractive and probably a useful research in technically developing regions.

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Department of Pharmacology
George Washington University
1339 H St. N.W.
Washington D.C.

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